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Review

Vitamin D and Maternal and Child Health: Overview and Implications for Dietary Requirements

Janet Y. Uriu-Adams, Sarah G. Obican and Carl L. Keen*

The essentiality of vitamin D for normal growth and development has been recognized for over 80 years, and vitamin D fortification programs have been in place in the United States for more than 70 years. Despite the above, vitamin D deficiency continues to be a common finding in certain population groups. Vitamin D deficiency has been suggested as a potential risk factor for the development of preeclampsia, and vitamin D deficiency during infancy and early childhood is associated with an increased risk for numerous skeletal disorders, as well as immunological and vascular abnormalities. Vitamin D deficiency can occur through multiple mechanisms including the consumption of diets low in this vitamin and inadequate exposure to environmental ultraviolet B rays. The potential value of vitamin D supplementation in high-risk pregnancies and during infancy and early childhood is discussed. Currently, there is vigorous debate concerning what constitutes appropriate vitamin D intakes during early development as exemplified by differing recommendations from the Institute of Medicine Dietary Reference Intake report and recent recommendations by the Endocrine Society. As is discussed, a major issue that needs to be resolved is what key biological endpoint should be used when making vitamin D recommendations for the pregnant woman and her offspring. **Birth Defects Research (Part C) 99:24–44, 2013.** © **2013 Wiley Periodicals, Inc.**

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INTRODUCTION

That an "antirachitic factor" (i.e., rickets preventative) is critical for early bone development has been recognized for over 100 years. In the early 1600s, a high percentage of children in England were found to have rickets (Chesney, 2012), a condition that is characterized by growth retardation and poor skeletal mineralization. As the growth plates of bones enlarge and the load on limbs increases, limbs become bowed resulting in mild to severe bone abnormalities of the legs, pelvis, ribs, and wrist. Rickets were particularly prevalent in large towns and industrialized regions, which often had hazy, smoggy, and polluted atmospheres due to coal mining and manufacturing. This epidemic compelled scientists to search for an "antirachitic factor." While on a medical mission to Asia in 1890, physician Theobald A. Palm observed that Japanese children were free of rickets. He noted that the biggest difference between England and Japan was that England had a variety of factors that prohibited the sun's rays from reaching the ground including smoke-laden and murky skies, high houses, and narrow streets, while opposite conditions were noted in the "Land of the Rising Sun" (Palm, 1888). Palm correctly speculated that sunlight might prevent rickets. That suboptimal diets could contribute to the occurrence of rickets was first suggested in 1889 by the work of Bland-Sutton, a London surgeon who reported that a metabolic bone disease in lion cubs at the London Zoo could be prevented by a diet supplement of goat meat, crushed bones, and cod liver oil (Chesney and Hedberg, 2010). The subsequent discovery that vitamin D was the major "antirachitic factor" in cod liver oil established the fact that this nutrient could cure or prevent rickets (McCollum et al., 1922).

Vitamin D is unique as it is the only vitamin recognized to date that in addition to being obtained from dietary sources, can be provided in significant amounts through synthetic pathways localized in skin, when 7-dehydrocholesterol reacts with environmental ultraviolet B (UVB) radiation to produce the

Janet Y. Uriu-Adams is from Department of Nutrition, University of California, Davis, Davis, California
Sarah G. Obican is from Department of Obstetrics and Gynecology, Columbia University, New York, New York
Carl L. Keen is from Department of Nutrition and Internal Medicine, University of California, Davis, Davis, California

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*Correspondence to: Carl L. Keen, Ph.D., Nutrition Department, University of California, Davis, One Shields Avenue, Davis, CA 95616. E-mail: clkeen@ucdavis.edu

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vitamin (previtamin D). Previtamin D isomerizes to vitamin D which is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D; $t^1/_2$ ~2–3 weeks), and further metabolized in the kidney by 1-α-hydroxylase (CYP27B1) to the bioactive hormone, 1,25$(OH)_2$D (calcitriol; $t^1/_2 < 4$ hr). Due to its relatively long half-life and the fact that the circulating form of vitamin D (25(OH)D) is considered to reflect total vitamin D exposure (e.g., vitamin D from food, supplements, and endogenous production), serum 25(OH)D concentrations are widely used as a marker of vitamin D status. Unless otherwise specified, the form of vitamin D reported in the literature cited below refers to 25(OH)D. Concentrations of 25(OH)D and other vitamin D metabolites in the plasma or serum are reported in the literature as nmol/l and ng/ml. To compare between studies, vitamin D can be converted as follows: 1 ng/ml = 2.5 nmol/l. In addition, vitamin D dietary recommendations are expressed in International Units (IU) where 1 μg vitamin D = 40 IU.

In the United States, the large-scale fortification of vitamin D in milk in 1933 greatly reduced the incidence of rickets throughout the country (National Institutes of Health State-of-the-Science Panel, 2007). In 1997, when the Food and Nutrition Board (FNB) established Dietary Reference Intakes (DRI) for vitamin D, the Adequate Intake (AI) and Tolerable Upper Intake Level (UL) recommendations for healthy adults were set at 200 IU/day and 2000 IU/day, respectively (Institute of Medicine, 1997). A Recommended Dietary Allowance (RDA) for vitamin D was not established at that time due to insufficient scientific data. The AI was based on the maintenance of serum 25(OH)D concentrations at or above 27.5 nmol/l (11 ng/ml) for most age groups. In 2011, the FNB re-evaluated vitamin D DRIs and established the Estimated Average Requirement (EAR), RDA, and UL for vitamin D for adults as 400, 600, and 4000 IU/day, respectively, based on the amounts needed for bone health outcomes (Institute of Medicine, 2011). Serum 25(OH)D concentrations of approximately 50 nmol/l (20 ng/ml) was associated with benefit for most of the population. The observation that there was a doubling in the estimated need for vitamin D in just a little over a decade underscores the fact that research in the area of vitamin D nutrition is vigorous, and in many ways still in its infancy. As is discussed below, there is a substantial body of research that has been reported over the past 15 years that supports the concept that dietary intakes of vitamin D higher than the 2011 EAR and RDA may result in some positive health effects exclusive of bone health. In the current study, we provide a brief review of some of the recent literature concerning the metabolism and functions of vitamin D, the potential developmental consequences of "vitamin D deficiency," and the implications of the above for current and future recommendations for vitamin D for women of child bearing age, infants, and children.

VITAMIN D DEFICIENCY—SCOPE OF THE PROBLEM

A range of cutoff values for 25(OH)D concentrations have been used in the literature to determine vitamin D sufficiency (>50 to >100 nmol/l) (Prentice, 2008), thus the definition of vitamin D insufficiency and deficiency varies depending on the study. In this review, cutoff levels determined and used by the authors are reported. While the cutoff for vitamin D deficiency varies, the presence of rickets is a well-defined clinical sign of the deficiency. The fortification of milk and other food products with vitamin D in many countries, such as the US, has greatly reduced the incidence of rickets, however, during the past decade there have been numerous reports showing that vitamin D deficiency is still widespread in the world affecting significant proportions of the population in developing as well as developed countries (Weisberg et al., 2004; Prentice, 2008). Disturbingly, the reported incidence of vitamin D deficiency is thought to be increasing in some areas (Prentice, 2008). The reasons for this putative increase in vitamin D deficiency are multifactorial, and have been postulated to include reduced sunlight exposure (clothing covering the body, use of sunscreens in response to fear of skin cancer, reduced time outdoors, sedentary lifestyle, pollution, and high levels of cloud coverage), and reduced intakes of vitamin D-rich foods. A recent meta-analysis reports that for all the regions studied (Japan, the US, Canada, Australia/New Zealand, and the United Kingdom), vitamin D intakes during pregnancy were below current recommendations (Blumfield et al., 2013).

As noted above, it is well recognized that severe vitamin D deficiency in children can cause rickets. In adults, suboptimal vitamin D status can lead to osteomalacia, a condition of defective bone mineralization. In addition to the classical bone abnormalities, vitamin D deficiency can result in hypocalcemia-induced seizures, pain, generalized muscle weakness, heart, and respiratory problems (Prentice, 2008). It is increasingly appreciated that in addition to bone, systems including the immune, cardiovascular, renal, muscular, pancreatic, integumentary, and neural systems can be affected by vitamin D (Rosen et al., 2012). Importantly, during the past decade, suboptimal vitamin D status has also been associated with an increased risk of several chronic diseases including cardiovascular disease (CVD), diabetes, cancer, arthritis, schizophrenia, and multiple sclerosis (Holick, 2004), although causal links between vitamin D insufficiency and the above diseases still need to be established. In many regards, the current nutrition controversies regarding vitamin D are reflective of ongoing debates in several scientific societies regarding what we mean by terms such as "requirement." Should nutritional requirements be set at a point where they ensure reproduction and survival of a species? Or should they be set at a point that "optimizes long-term health" and reduces ones' risk for age-related chronic diseases? From

the perspective of a teratologist, should they be set at a point that allows for normal development in a healthy environment, e.g. for the "healthy population"? Or should they take into consideration the potential risk for common environmental insults, societal behaviors, the presence of maternal disease, genetics, and the developmental origins of adult disease? Like medicine, nutrition is slowly moving away from the "one size fits all" approach to one that takes into account the particular genetic makeup and lifestyles of the individual, with the goal to manage and optimize health through tailored medicine and nutrition. These are issues that merit considerable discussion by several scientific disciplines including nutrition, toxicology, and teratology.

VITAMIN D METABOLISM

The subcutaneous synthesis of previtamin D3 from 7-dehydrocholesterol upon UVB radiation is a major source of the vitamin. As mentioned above, previtamin D3 isomerizes to vitamin D which is first hydroxylated in the liver to 25(OH)D, then hydroxylated in the kidney by 1-α-hydroxylase (CYP27B1) to the bioactive hormone, 1,25$(OH)_2$D. Vitamin D binding protein is the major carrier of vitamin D metabolites in the circulation, with some bound to albumin and lipoproteins (Dusso et al., 2005). In vitamin D deficiency, decreased absorption of calcium and phosphorus increases parathyroid hormone (PTH) secretion which mobilizes calcium from the skeleton in an attempt to maintain homeostasis. PTH increases CYP27B1 expression leading to an increase in bioactive 1,25$(OH)_2$D (Adams and Hewison, 2012). In contrast, fibroblast growth factor 23 (FGF23) decreases CYP27B1 expression. Vitamin D plays a critical role in skeletal mineralization by acting in concert with PTH or FGF23 to regulate calcium and phosphorus homeostasis by altering uptake, turnover, and excretion in the intestine, bone, and kidney. In addition to the classical role of vitamin D in bone mineralization, 1,25$(OH)_2$D can bind to the vitamin D receptor (VDR), a nuclear transcription factor found in nearly every cell, which can directly, or in concert with nuclear hormone receptors such as the retinoid X receptor (RXR), bind to vitamin D response elements in the promoter of genes resulting in the transcriptional regulation of 3–10% of the human genome (Rosen et al., 2012; Zhu et al., in press).

VITAMIN D SOURCES

Vitamin D is a fat-soluble vitamin that possesses hormone-like actions. Vitamin D2 (ergocalciferol) can be obtained from a wide variety of plants and fungi, with UV light-exposed mushrooms being particularly rich in this nutrient (Liu, 2012). Vitamin D3 (cholecalciferol) occurs naturally in relatively few foods, such as some fatty fish and egg yolks, but in many countries it can be present in relatively high amounts in certain fortified foods including milk and cereals, as well as in dietary supplements. Table 1 lists the vitamin D content in a number of select dietary sources. Unfortified conventional foods in typical Western diets provide on the order of 100 IU (2.5 μg) of vitamin D per day (Institute of Medicine, 1997). A recent study of vitamin D intake in individuals in the US and Canada suggests that less than 2% of the participants in all age groups met the 2011 RDA for vitamin D from foods (Hill et al., 2012). Similar reports that adequate intake of vitamin D is not likely to be achieved through typical dietary intakes of vitamin D from unfortified foods are available for Australia and Europe (Nowson and Margerison, 2002; Liu, 2012; Mensink et al., 2013). In the 1930s, a milk fortification program was implemented in the United States to combat rickets, then a major public health problem. Currently, the majority of the US retail milk supply is voluntarily fortified, generally with vitamin D3 (100 IU/cup, $\sim$10 μg/quart), although a nationwide sampling of milk shows that there is a high variability in vitamin D content (Patterson et al., 2010). Additionally, there is a mandatory fortification of infant formula (40–100 IU/100 kcal). Typical multivitamin supplements in the US contain around 200–400 IU (5–10 μg) of vitamin D, but supplements containing an excess of 40,000 IU (1000 μg) are becoming increasingly common (Hathcock et al., 2007). To put the above numbers into perspective, it has been estimated that chronic exposure to sunlight in outdoor workers can result in serum 25(OH)D concentrations that are similar to those obtained with oral intakes of 2800–5000 IU (70–125 μg) of vitamin D per day (Barger-Lux and Heaney, 2002). It has been recently estimated that about 40% of women (25–50 years old) in the US do not take vitamin D-containing supplements (Gordon et al., 2012). Several studies have shown that vitamin D intake from food and supplements is below the current RDA in 20–49 year old white women (293.2 ± 10.48 IU/day; 7.33 ± 0.262 μg/day) and even lower in African American women (229.2 ± 7.84 IU/day; 5.73 ± 0.196 μg/day) (Calvo et al., 2004; Harris, 2006). The lower vitamin D intakes observed in African Americans may be due in part, to lactose intolerance and avoidance of dairy products (Moore et al., 2005).

In many populations, the major source of vitamin D is that which is generated in the skin by exposure to sunlight, i.e. UVB radiation can convert 7-dehydrocholesterol to previtamin D. Before humans wore clothes, worked in offices, led sedentary lifestyles and used sunscreen, individuals had significantly greater exposure to sunlight. Individuals who spend large amounts of time outdoors (landscaping, construction work, farming, or recreation) have 25(OH)D concentrations of 122 nmol/l (48.8 ng/ml) on average (Barger-Lux and Heaney, 2002). These data could be interpreted by some that, teleologically, natural exposure to sunlight and circulating levels of 25(OH)D above 100 nmol/l (40 ng/ml), are compatible with human survival. Serum 25(OH)D concentrations above

TABLE 1. Common Dietary Sources of Vitamin D[a]

Food	IUs per serving	Percent DV
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115–124	29–31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75–1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

IUs = International Units; DV = Daily Value. DVs were developed by the US Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for vitamin D was set at 400 IU for adults and children age 4 and older. Food labels, however, are not required to list vitamin D content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.
[a]Office of Dietary Supplements, National Institutes of Health: Dietary Supplement Fact Sheet: Vitamin D. http://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/#h3 (accessed February 6, 2013).

200 nmol/l (80 ng/ml) can be common among healthy persons with ample sun exposure (Vieth, 1999). Concentrations of 25(OH)D in these same individuals decreased to 74 nmol/l (29.6 ng/ml) in late winter (40% reduction) indicating that intensive sun exposure does not maintain high 25(OH)D concentrations through winter. Currently, there is considerable debate about what serum 25(OH)D concentrations are associated with vitamin D deficiency, insufficiency, sufficiency, and potential adverse effects (Table 2).

DIVERSE FACTORS INFLUENCE VITAMIN D STATUS

There are numerous factors that can affect the efficiency of endogenous vitamin D production (Fig. 1). A high degree of melanin-rich, dark skin can absorb UVB rays and reduce sunlight penetration leading to a decrease in vitamin D production. Data from the third National Health and Nutrition Examination Survey (1988–1994) showed that 42.4% of African American women and 4.2% of white women of reproductive age were characterized as having hypovitaminosis D defined as serum 25(OH)D $\leq$ 37.5 nmol/l ($\leq$ 15 ng/ml) (Nesby-O'Dell et al., 2002). Of the African American women who consumed 200 IU (5 μg) of vitamin D as supplements, 28.2% had hypovitaminosis D. While African Americans have lower vitamin D levels, they do not, as a group, have lower bone densities suggesting that their PTH response may have adapted to lower vitamin D or

TABLE 2. 25(OH)D Concentrations (expressed as nmol/l and ng/ml) Used to Define Vitamin D Status as of 2013

Definition of vitamin D status (based on 25(OH)D concentrations)	Institute of Medicine[a]		Endocrine Society[b]	
Deficient	<30 nmol/l	<12 ng/ml	<50 nmol/l	<20 ng/ml
Insufficient	30–50 nmol/l	12–20 ng/ml	52.5–72.5 nmol/l	21–29 ng/ml
Sufficient	>50 nmol/l	>20 ng/ml	>75 nmol/l	>30 ng/ml
Potential adverse effects	>125 nmol/l	>50 ng/ml	No cutoff value defined	

[a]Institute of Medicine, 2011.
[b]Holick et al., 2011.

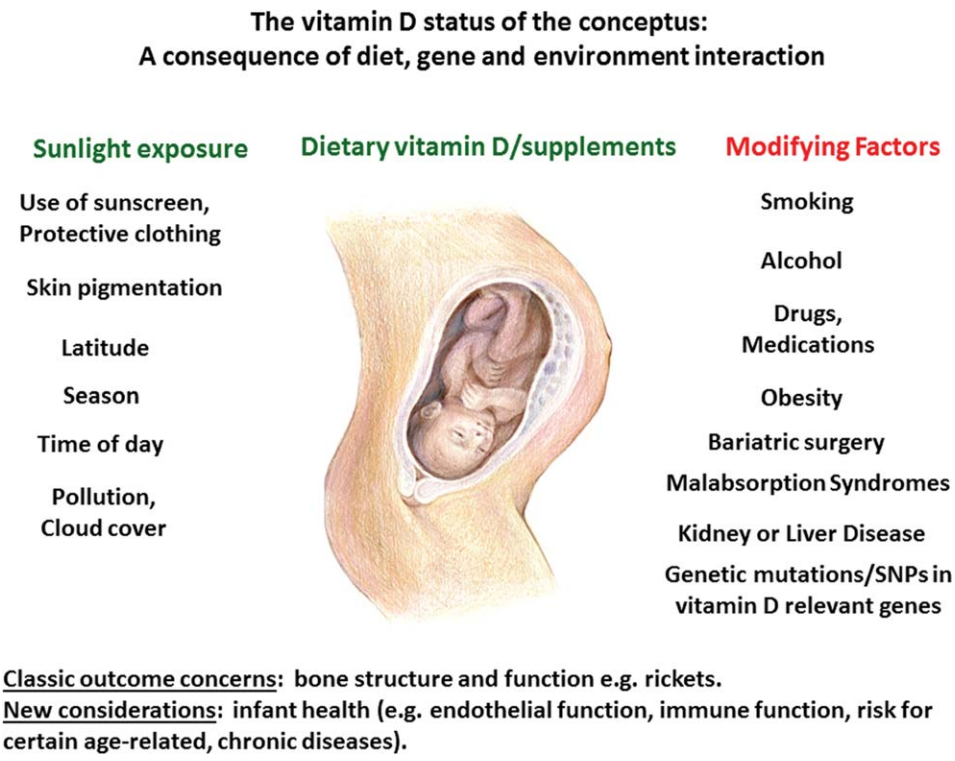

Figure 1. The multifactorial interplay of factors that influence the vitamin D status of the developing conceptus.

there is a skeletal resistance to PTH such that there is lower bone resorption (Harris, 2006). Whether metabolic adaptation occurs in individuals with increased skin pigmentation such that lower baseline vitamin D levels are required for some adverse health outcomes to occur is unknown. However, what is evident is that higher frequencies of rickets are observed in dark-skinned individuals (Brannon and Picciano, 2011) indicating that the developing fetus is affected by maternal vitamin D status.

A number of factors can decrease the availability of direct sunlight including the time of day and substances such as pollutants and cloud matter which can absorb, scatter, or reflect UVB radiation resulting in a reduction in endogenous vitamin D production (Tsiaras and Weinstock, 2011). Higher rates of suboptimal vitamin D status are noted in individuals living at high latitude, in the winter season, and in geographical regions with significant pollution. Changes in public perceptions regarding what are good or bad foods (e.g., milk, margarine, eggs), what one should do to minimize health risks associated with excessive UV radiation (e.g., the use of sun-blocking agents), and covered dressing styles because of ethnic or religious principles (e.g., the use of hijab, burqa), can contribute to an increased risk for the classical signs of vitamin D deficiency. In Turkey, 21.3% of adolescent girls had vitamin D deficiency defined as 25(OH)D $<$ 25 nmol/l ($<$ 10 ng/ml) whereas 50% of girls who wore covered dress for religious reasons were characterized as vitamin D deficient (Hatun et al., 2005).

Obesity has been associated with low vitamin D status. Obese individuals have similar vitamin D3 production in response to UV radiation as lean individuals but they have lower circulating vitamin D concentrations due in part to sequestration of vitamin D in adipose tissue (Wortsman et al., 2000). Recent reports suggest that the adipocyte is also a target of vitamin D. Adipocytes express both the VDR and 1-α-hydroxylase genes and vitamin D influences the function and differentiation of adipose tissue (Ding et al., 2012). Thus low circulating vitamin D may affect adipose tissue metabolism. Elderly populations have been characterized with low vitamin D status due in part to reduced time outdoors, poor vitamin D intake, impaired renal function, and a lower endogenous production of vitamin D (MacLaughlin and Holick, 1985; Mosekilde, 2005; Institute of Medicine, 2011). Vitamin D deficiency is also thought to occur with a higher than normal frequency in individuals with intestinal malabsorptive syndromes including celiac disease, liver and renal diseases, after bariatric surgery, and following the administration of select drugs such as phenobarbital and phenytoin and those used in HIV antiviral therapy, colorectal cancer chemotherapies, and antiepileptic treatment (Vidailhet et al., 2012). The extent to which an individual's genetic background affects their susceptibility to vitamin D deficiency has recently received considerable attention as there is increasing evidence that in addition to mutations in the VDR gene which leads to rickets (Saijo et al., 1991), certain single nucleotide

polymorphisms (SNPs) in vitamin D metabolism genes are associated with circulating vitamin D levels, and that the presence of some SNPs can be associated with an increased risk for select diseases (Bu et al., 2010; Wang et al., 2010; in press). Given that breast milk is typically low in vitamin D, in the absence of supplements, breastfed infants typically have a higher risk of suboptimal vitamin D status than do formula-fed infants (see below).

Similar to many other essential nutrients, it has been reported that circulating vitamin D concentrations can decrease as a consequence of an acute-phase response (APR) as in the study by Louw et al. (1992), where the APR was induced by surgery, or the study of ankylosing spondylitis (an inflammatory rheumatic disease) where 25(OH)D concentrations were inversely related to C-reactive protein (CRP), an index of inflammation and disease activity (Erten et al., 2013). As has been discussed elsewhere, APR-induced changes in circulating nutrient concentrations can contribute to abnormal embryonic and fetal development (Uriu-Adams and Keen, 2010). The extent to which low levels may persist in the event of chronic APR has not been extensively studied. Alcoholism can be viewed as a chronic APR condition. Alcoholic patients in a hospitalized or outpatient clinic setting have a high prevalence (38–55%) of vitamin D deficiency defined as serum 25(OH)D $<$ 30 nmol/l ($<$ 12 ng/ml) (Bang et al., 2009; Malham et al., 2011; Wijnia et al., 2013). In a rodent model, ethanol ingestion during pregnancy resulted in low hepatic concentrations of 25(OH)D in the pups compared to pups from control dams (Milne and Baran, 1985). After confounder adjustment, in a population of pregnant women in Ukraine who consumed moderate to high amounts of alcohol, preliminary data show that each ounce of alcohol consumed per drinking day in the 2 weeks prior to the time of enrollment was associated with a decrease in plasma 25(OH)D of 6 nmol/l (2.4 ng/ml) (Carlson et al., 2012). However, alcohol consumption during pregnancy did not increase the risk of vitamin D deficiency in Belgian women (Vandevijvere et al., 2012). Smoking has also been associated with a decrease in serum 25(OH)D concentrations (Vandevijvere et al., 2012; Bjorn Jensen et al., 2013; Andersen et al., in press). Thus, diverse factors can impact maternal and fetal vitamin D status (Fig. 1).

VITAMIN D ASSESSMENT AND DIETARY RECOMMENDATIONS

It is generally accepted that the serum concentration of 25(OH)D can be a useful biomarker of vitamin D status; however, the definition of vitamin D adequacy is a matter of vigorous debate (Table 2). In 2011, the Institute of Medicine (IOM) defined vitamin D sufficiency as concentrations of 25(OH)D $>$ 50 nmol/l ($>$20 ng/ml) (Institute of Medicine, 2011), whereas the Endocrine Society defined vitamin D sufficiency as concentrations of 25(OH)D $>$ 75 nmol/l ($>$30 ng/ml) (Hollick et al., 2011). In the 2011 report, the IOM used 25(OH)D concentrations $<$ 30 nmol/l ($<$12 ng/ml) as their cutoff for vitamin D deficiency noting that 25(OH)D concentrations less than this increases the risk for vitamin D deficiency-induced rickets, with vitamin D insufficiency ranging between 30 and 50 nmol/l (12–20 ng/ml). In the 2011 report, the IOM stated that serum 25(OH)D levels $>$ 75 nmol/l ($>$ 30 ng/ml) are not consistently associated with increased benefit and that levels $>$ 125 nmol/l ($>$ 50 ng/ml) might be associated with adverse effects (Institute of Medicine, 2011). The Endocrine Society currently defines vitamin D deficiency as 25(OH)D concentrations below 50 nmol/l ($<$20 ng/ml) and vitamin D insufficiency is defined as 25(OH)D concentrations of 52.5 to 72.5 nmol/l (21–29 ng/ml) (Hollick et al., 2011). Thus, when one asks the question, "How frequently does vitamin D deficiency occur?" the answer is in part driven by the criteria one uses to determine vitamin D adequacy. This is important to keep in mind when comparing and contrasting the different incidences of suboptimal vitamin D that are reported from different countries, and is particularly important when assessing the conclusions of papers based on meta-analyses.

Recommendations for dietary intake of vitamin D vary from country to country as well as within countries (Table 3). The observation that in 2011 the IOM published new DRIs for vitamin D that increased the RDA from 400 (the 1997 recommendation) to 600 IU/day for pregnant and lactating mothers (Institute of Medicine, 2011) underscores the rapidly evolving concepts we have regarding the nutritional needs for vitamin D. Importantly, the 2011 IOM report focused on the well-established calciotropic and skeletal effects of vitamin D, and not on other non-classical actions of vitamin D. The 2011 IOM report increased the UL from 2000 to 4000 IU/day.

In contrast to the most recent IOM recommendations, the Endocrine Society (Table 3) recommends at least 600 IU/day for pregnant and lactating women and suggests that for individuals at risk for vitamin D deficiency, 1500 to 2000 IU/day may be needed to maintain a blood level of 25(OH)D above 75 nmol/l ($>$30 ng/ml) (Holick et al., 2011). We submit that the suggestion that certain subgroups of apparently healthy individuals may have a higher requirement for vitamin D than other apparently healthy subgroups is analogous to the case for folate where dietary folate recommendations were increased for women to reduce their risk for pregnancy complications (e.g., neural tube defects) rather than to directly treat a folate deficiency. For obese children and adults, the Endocrine Society noted that 2 to 3 times more vitamin D for their age group may be needed to satisfy their body's vitamin D requirement. The Endocrine Society also recommended an upper limit of 4000 IU/day for everyone over 8 years of age, with the caveat that higher levels may be needed to

TABLE 3. Examples of Dietary Recommendations for Vitamin D

Life stage group	1997 IOM Adequate Intake (AI)[a]	1997 IOM Tolerable Upper Intake Level (UL)[a]	2011 IOM Recommended Dietary Allowance (RDA)[b]	2011 IOM Tolerable Upper Intake Level (UL)[b]	2011 Endocrine Society Daily Requirement for patients at risk for vitamin D deficiency[c]	2011 Endocrine Society Tolerable Upper Intake Level for patients at risk for vitamin D deficiency[c]	Adequate Intake values for Australia and New Zealand (AI)	Upper Level of Intake Values for Australia and New Zealand (UL)
0 through 6 months	200	1,000	400 (AI)	1,000	400–1,000	2,000	200	1,000
7 through 12 months	200	1,000	400 (AI)	1,500	400–1,000	2,000	200	1,000
1 through 3 years	200	2,000	600	2,500	600–1,000	4,000	200	3,200
4 through 8 years	200	2,000	600	3,000	600–1,000	4,000	200	3,200
9 through 18 years	200	2,000	600	4,000	600–1,000	4,000	200	3,200
19 through 50 years	200	2,000	600	4,000	1,500–2,000	10,000	200	3,200
51 through 70 years	400	2,000	600	4,000	1,500–2,000	10,000	400	3,200
> 70 years	600	2,000	800	4,000	1,500–2,000	10,000	600	3,200
Pregnancy								
≤18 years	200	2,000	600	4,000	600–1,000	4,000	200	3,200
19 through 50 years	200	2,000	600	4,000	1,500–2,000	10,000	200	3,200
Lactation								
≤18 years	200	2,000	600	4,000	600–1,000	4,000	200	3,200
19 through 50 years	200	2,000	600	4,000	1,500–2,000	10,000	200	3,200

[a]Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. 1997. Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D and Fluoride. The National Academies Press: Washington, D.C.
[b]Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, in Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, et al., editors. 2011, The National Academies Press: Washington, D.C.
[c]Holick et al., 2011.
[d]Ministry of Health, National Health and Medical Research Council, Australian Government. Nutrient Reference Values for Australia and New Zealand. http://www.health.govt.nz/publication/nutrient-reference-values-australia-and-new-zealand [accessed January 29, 2013].

overcome vitamin D deficiency. There is an ongoing and robust debate about whether the RDA and UL for vitamin D should be further increased. There is evidence that the mother's vitamin D status will affect breast milk vitamin D concentrations, thus impacting the infant's vitamin D status (discussed below). Several reports show that high-dose vitamin D supplementation can increase maternal and breast milk vitamin D status. The American Pediatrics Society recommends vitamin D supplementation for exclusively breast-fed infants. The Endocrine Society recommends dietary vitamin D intake of infants to be 400 IU/day; however, if mothers choose not to supplement their infant, the Society recommends that the mother increase her vitamin D intake to 4000 to 6000 IU/day (Holick et al., 2011). As is discussed below, there is emerging evidence that vitamin D can affect the programming of metabolism during in utero development, influencing the risk for certain diseases later in life (Sundar and Rahman, 2011; Crozier et al., 2012; Hossein-nezhad and Holick, 2012). While it is well accepted that the developing fetus should have optimal vitamin D status, whether optimal vitamin D status is achieved via vitamin D supplementation to the mother or infant or both is a matter of debate.

AN EVOLUTION IN THE DIETARY RECOMMENDATIONS FOR VITAMIN D

In the United States, current DRIs are based on specified indicators or markers that are deemed to be the most appropriate to determine the risk of deficiency for that nutrient, or to determine the risk of chronic degenerative disease for that nutrient. In the most recent FNB review of vitamin D requirements, the selected criterion for the DRIs for vitamin D was bone health (Institute of Medicine, 2011). Figure 2 depicts the typical and hypothetical DRI curves for vitamin D intake based on a single outcome such as bone health (Fig. 2A) as well as based on nonskeletal outcomes such as endothelial health (Fig. 2B). As defined by the IOM, the EAR reflects the estimated median requirement and is particularly appropriate for applications related to planning and assessing intakes for groups of persons. The RDA is derived from the EAR and meets or exceeds the requirement for 97.5 percent of the healthy population. The UL is the highest average daily intake level that is likely to pose no risk of adverse effects to almost all individuals in the general population. While the typical DRI curve depicts a potential increase in the risk of adverse effects as intake increases above the UL, the actual shape of the curve is under debate. The IOM has set the UL at 4000 IU/day. The type of curve shown reflects what is thought to be needed for the "typical healthy population." The idea that different levels of dietary intake of vitamin D are needed to reduce the risk of non-skeletal health outcomes is an active area of research. Well-designed clinical trials are needed to clarify this issue.

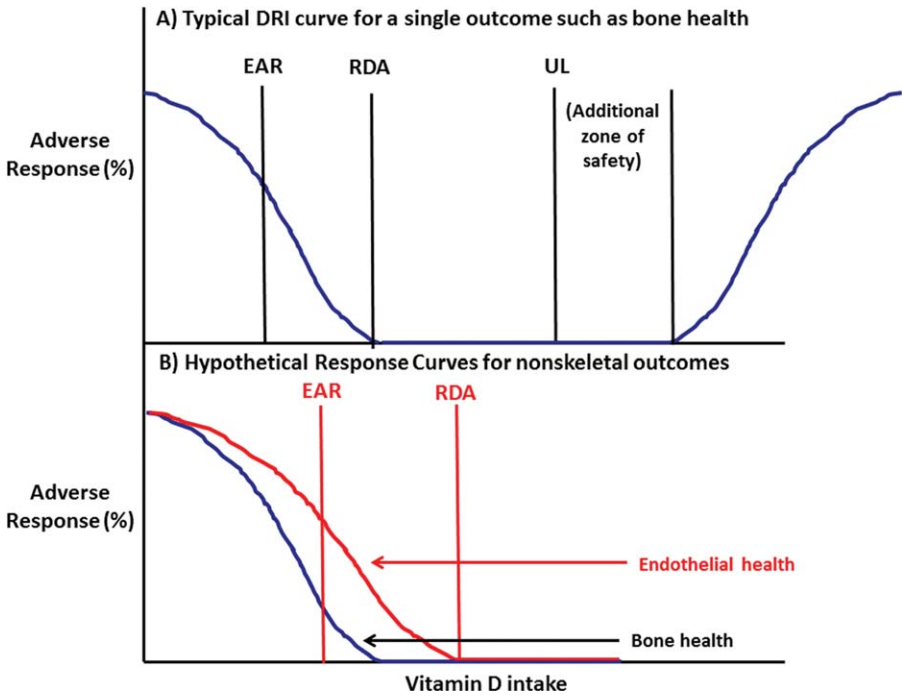

Figure 2. Dietary recommended intakes: typical versus hypothetical. Typical DRI curve for vitamin D intake based on a single outcome such as bone health (**A**). EAR: Estimated Average Requirement; RDA: Recommended Dietary Allowance; UL: Tolerable Upper Level. Hypothetical response curve for vitamin D intake needed to achieve the EAR and RDA for a nonskeletal outcome such as endothelial health. In this case, the hypothetical intakes of vitamin D that are needed for vascular health exceed those needed for bone health. The Tolerable Upper Intake Level (UL) is not depicted in this hypothetical response curve.

VITAMIN D IN PREGNANCY, PLACENTA, AND VASCULAR FUNCTION

During pregnancy, there is a threefold increase in $1,25(OH)_2D$, the majority likely from kidney production with some coming from placental origin (Hollis et al., 2011; Liu and Hewison, 2011). $1,25(OH)_2D$ does not readily cross the placenta, whereas 25(OH)D does; thus maternal and fetal levels of 25(OH)D correlate (Liu and Hewison, 2011). In mice null for VDR or CYP27B1, there is a markedly reduced female fertility (Yoshizawa et al., 1997). However, in VDR knockout mice, fertility can be restored by feeding a high calcium diet, thus the direct effects of $1,25(OH)_2D$ on fertility are unknown. When a vitamin D deficient diet is fed, fertility rates and litter size are reduced in rodents. Interestingly, in vitro fertilization–embryo transfer has been reported to be more successful in women with high vitamin D status (serum or follicular fluid) compared to individuals with low status (Ozkan et al., 2010; Liu and Hewison, 2011).

Consequences of low maternal vitamin D status include adverse health effects for the mother, infant, and developing child. Maternal vitamin D deficiency occurs worldwide, even in sunny climates, and is a significant public health issue with prevalence rates ranging from 5 to 89% depending on the cutoff value used (Bodnar et al., 2007b; Greer, 2008; Prentice, 2008; Sahu et al., 2009; Yu et al., 2009; Hamilton et al., 2010; Agarwal and Arya, 2011; Hossain et al., 2011; Johnson et al., 2011; Vandevijvere et al., 2012; McAree et al., 2013; Andersen et al., in press). In a recent study in the US, an estimated 5 to 29% of pregnant women had inadequate vitamin D status with a higher prevalence in African Americans who are at a higher risk of vitamin D deficiency due to increased skin pigmentation which can decrease endogenous vitamin D production (Brannon and Picciano, 2011). In the US, 29.2% of African American women and 5% of white women were classified as vitamin D deficient (25(OH)D <37.5 nmol/l; <15 ng/ml) while 54.1% of African American women and 42.1% of white women were designated as vitamin D insufficient (25(OH)D $= 37.5–80$ nmol/l; 15–32 ng/ml) (Bodnar et al., 2007b). In keeping with the above, 45.6% of black neonates versus 9.7% of white neonates were reported to be vitamin D deficient. Vitamin D insufficiency was reported for 46.8% and 56.4% of black and white neonates, respectively (Bodnar et al., 2007b). These data support the concept that there is a very high prevalence of vitamin D insufficiency in US pregnant women and neonates despite the reported widespread use of prenatal vitamins. The above begs the question of whether the level of vitamin D in prenatal supplements is sufficient to sustain adequate vitamin D nutriture. Also of concern is whether vitamin supplements actually contain the labeled content of vitamin D. Vitamin supplements are not regulated by the Food and Drug Administration and content provided in a supplement can vary significantly from the claimed dosage (Garg et al., 2013).

A number of recent observational reports indicate that low vitamin D concentrations in the mother are associated with an increased risk of preeclampsia (defined as new onset hypertension and proteinuria after 20 weeks of gestation). Preeclampsia affects 3 to 5% of all pregnancies worldwide and is a leading cause of maternal and fetal morbidity and mortality. Early-onset severe preeclampsia (EOSPE) has been reported to contribute to 15% of preterm births (Robinson et al., 2010). Low maternal vitamin D intakes and low maternal vitamin D concentrations during pregnancy have been associated with an increased risk for preeclampsia in some (Bodnar et al., 2007a; Haugen et al., 2009) but not in all studies (Oken et al., 2007; Powe et al., 2010). As data from studies are conflicting, meta-analysis has been used to estimate the association between maternal vitamin D status and adverse pregnancy outcomes. From a meta-analysis of 24 observational studies, Wei et al. reported that mothers who had 25(OH)D levels <50 nmol/l (<20 ng/ml), had a twofold increase in the risk of preeclampsia (Wei et al., 2013). In overweight and obese pregnant women with body mass index (BMI) of 24 to 38, EOSPE African American and white women had low vitamin D status compared to respective healthy controls (Robinson et al., 2010). African American women with EOSPE had the lowest vitamin D concentrations of the four groups. Interestingly, African American controls in this study had lower vitamin D concentrations than EOSPE white women indicating that the actual level of circulating vitamin D is not necessarily predictive of EOSPE occurrence. As mentioned above, it is unclear whether there is a lower threshold for vitamin D deficiency-induced disease in African Americans. Robinson et al. noted that patients with EOSPE who delivered small-for-gestational-age babies had lower mid-gestation 25(OH)D concentrations than EOSPE mothers with normal weight babies (Robinson et al., 2011). These studies are observational in nature; longitudinal clinical trials are needed to assess whether vitamin D has an active role in the development or progression of preeclampsia. In addition, preeclampsia has recently been reported to be a risk factor for the development of CVD and metabolic syndrome later in life with a five- to sevenfold risk of CVD associated with severe and/or early-onset preeclampsia (Giguere et al., 2012); thus, it will be important to identify genetic, environmental, and dietary factors that can contribute to the development of preeclampsia in order to prevent or treat this disorder.

How might vitamin D affect preeclampsia? Preeclampsia is a condition that is characterized by abnormal or inadequate placental invasion, development and remodeling, placental ischemia/hypoxia, increases in pro-inflammatory cytokines, increased oxidative stress, changes in nitric oxide (NO), and

endothelial dysfunction. It is biologically plausible that vitamin D may act at several of these steps. Vitamin D is important in cell signaling and placental gene regulation and expression (Evans et al., 2004; Barrera et al., 2008). Using site-directed mutagenesis, Cardus et al. showed that the vascular endothelial growth factor (VEGF) gene contains two VDR binding sites in the promoter (Cardus et al., 2009). In studies using cord blood endothelial colony-forming cells, $1,25(OH)_2D$ increased VEGF expression and promoted angiogenesis in vitro (Grundmann et al., 2012) while VEGF expression is decreased in preeclamptic placenta (Andraweera et al., 2012). The placenta expresses both the VDR as well as the 1-α-hydroxylase gene (CYP27B1) that converts 25(OH)D to 1,25-(OH)(2)D, the bioactive form of vitamin D which can be utilized locally or released into circulation as a paracrine factor. It is currently thought that placental production of bioactive vitamin D contributes to an immunoregulatory rather than a calcium homeostasis function (Adams and Hewison, 2012). Syncytiotrophoblast cells isolated from placentas in preeclamptic pregnancies have decreased expression and activity of the 1-α-hydroxylase gene compared to normal placentas (Diaz et al., 2002), which if it occurs early in pregnancy may contribute to abnormal placentation.

Studies have shown that in vitro exposure to vitamin D can improve endothelium-dependent arterial relaxation and reduce oxidative stress in renal arteries from hypertensive patients (Dong et al., 2012). Six months of oral $1,25(OH)_2D$ treatment reversed the renovascular dysfunction in spontaneously hypertensive (SHR) rodents supporting the idea that in vivo exposure to vitamin D improves vascular endothelial function (Dong et al., 2012). Similarly, 16 weeks of vitamin D supplementation (60,000 IU/month) significantly improved flow-mediated dilation in African Americans compared to placebo (Harris et al., 2011). Whether vitamin D positively contributes to reducing hypertension in pregnancy is unknown. Bodnar et al. have reported a 2.4-fold increased risk of preeclampsia for every serum 25(OH)D level decline of 50 nmol/l (20 ng/ml) (Bodnar et al., 2007a) although other studies have found no association (Brannon and Picciano, 2011). In women who took 400 to 600 IU (10–15 μg) vitamin D/day compared to no supplement, there was a reported 27% decrease in risk of preeclampsia (Haugen et al., 2009). Diastolic blood pressure was decreased by 8 mm Hg with 1200 IU (30 μg) vitamin D plus 375 mg calcium/day starting at 20 weeks of gestation, but this treatment did not influence the occurrence of preeclampsia in a non-placebo controlled randomized trial (Marya et al., 1987). Additional studies are needed to clarify whether low maternal vitamin D leads to increased risk of preeclampsia, and most importantly, if supplemental vitamin D can reduce the risk for this disorder.

The immunomodulatory effects of vitamin D in the placenta are being increasingly studied. Maternal decidua and placental trophoblasts express 1-α-hydroxylase (CYP27B1) early in gestation and are able to produce bioactive vitamin D (Christakos and DeLuca, 2011; Liu and Hewison, 2011). It has been suggested that preeclampsia is mediated by a shift toward more dominant T helper type 2 (Th2) cytokine responses, which may be reduced by vitamin D supplementation (Hypponen, 2011). Liu et al. have reported that $1,25(OH)_2D$ induces the antimicrobial protein cathelicidin and enhances the antibacterial response in trophoblastic cells suggesting that the local production of vitamin D may activate the innate immune response in the placenta (Liu et al., 2009, 2011). Preterm and early term delivery has been linked to infection and the presence of inflammatory cytokines; maternal vitamin D deficiency has been reported to be associated with these adverse pregnancy outcomes in some, but not all, studies. Maternal vitamin D insufficiency has been consistently associated with increased rates of bacterial vaginosis (Bodnar et al., 2009; Hensel et al., 2011), an imbalance of naturally occurring microflora in the vagina which can lead to infections and inflammation in other tissues with release of inflammatory cytokines. The induction of cathelicidin in human trophoblast cells by vitamin D promotes the intracellular killing of *Escherichia coli* (Liu and Hewison, 2011). Trophoblast cells from mice null for VDR or 1-α-hydroxylase genes show increased inflammatory response to bacterial components while treatment of wild type cells with vitamin D suppresses the inflammatory response (Urrutia and Thorp, 2012). As anti-infective factors are important for maternal and fetal health, it will be important to determine the extent to which placental production of vitamin D plays a role in preventing infections.

Additional adverse pregnancy outcomes that have been linked to maternal vitamin D deficiency include an increased incidence of low birth weight babies, and an increased risk for gestational diabetes, preterm delivery, obstructed labor, cesarean delivery, and miscarriage in some, but not all, studies (Brannon et al., 2008; Bodnar et al., 2009; Dror and Allen, 2010; Dror et al., 2011; Hollis et al., 2011; Lau et al., 2011; Poel et al., 2012; Thorne-Lyman and Fawzi, 2012; Wei et al., in press). Genetic variability of the VDR has been strongly associated with infant birth weight among non-Hispanic black (who have higher rates of preterm birth and low birth weight infants), but not non-Hispanic white, women (Swamy et al., 2011). However, due to contradictory evidence and limited randomized clinical trials, whether vitamin D is causally linked to these conditions remains to be firmly established (Brannon and Picciano, 2011; Urrutia and Thorp, 2012).

Several studies have evaluated the effects of vitamin D supplementation during pregnancy on diverse outcomes. The vitamin D supplementation regimens used in studies vary widely with some administering

400 to 4000 IU (10–100 μg) per day and others giving one-time doses of 100,000 to 200,000 IU (2500–5000 μg). Still unclear is the identification of a minimum dose that will be effective in improving pregnancy outcomes that does not invoke toxicity. In India, vitamin D supplementation [one dose of 60,000 IU (1500 μg) in the 2nd trimester or two doses of 120,000 IU (3000 μg) in the 2nd and 3rd trimesters] improved anthropometry in the newborn compared to no treatment which persisted until 9 months of age (Kalra et al., 2012). Unclear is the extent to which vitamin D supplementation-induced changes in calcium absorption or metabolism may contribute to any effects or associations noted. A recent analysis of two randomized controlled trial (RCTs) of 2000 and 4000 IU (50 and 100 μg) vitamin D supplementation during pregnancy showed no effect of supplementation on pregnancy co-morbidities when women who did not adhere to the protocol were included (intent-to-treat basis) (Wagner et al., in press). However, when maternal 25(OH)D concentrations were used, women who had 25(OH)D concentrations $<$80 nmol/l ($<$32 ng/ml) had significantly higher combined comorbidities rates compared to women with $>$80 nmol/l ($>$32 ng/ml). Of the comorbidities, rates for hypertensive disorders, infection and preterm birth without preeclampsia tended to be higher in the lower versus the higher serum vitamin D groups (p-values = 0.11, 0.070, and 0.072, respectively) (Wagner et al., in press).

INFANT

Plasma concentrations of 25(OH)D and 1,25(OH)D2 decrease ~35% and 60%, respectively, through the first month in exclusively breast-fed infants (Hoogenboezem et al., 1989), with season and degree of skin pigmentation affecting levels (Greer, 2008; Brannon and Picciano, 2011). At the end of winter, 70% of infants had cord blood 25(OH)D less than 20 nmol/l (8 ng/ml) (Pawley and Bishop, 2004). Even in sunny climates, a very high percentage of mothers and infants have been reported to have vitamin D deficiency defined as $<$ 50 nmol/l ($<$ 20 ng/ml) due in part to covered dressing style, low consumption of dairy products, and lack of multivitamin use during gestation (Halicioglu et al., 2012). In the United Kingdom, black premature infants ($<$32 weeks gestational age) had lower cord blood 25(OH)D compared to white infants (Hanson et al., 2011). A high prevalence of vitamin D insufficiency in pregnant women and their neonates was also observed in the US, with a higher prevalence in black populations than in white populations (Bodnar et al., 2007b). While full-blown rickets generally develop between the ages of 6 to 18 months in infants in the US (Greer, 2008), low vitamin D in Turkish mothers with osteomalacia was associated with clinical indices in the neonates that were consistent with rickets such as the presence of craniotabes (Yorifuji et al., 2008). Neonatal hypocalcemia, convulsions, and heart failure have also been reported in exclusively breast-fed, at-risk ethnic minority infants with very low vitamin D levels (Camadoo et al., 2007; Maiya et al., 2008). In infants and toddlers with vitamin D deficiency rickets, an intramuscular injection of 250 μg vitamin D (10,000 IU) per kg normalized serum calcium, phosphorus, and 25(OH)D concentrations at one month, and by three months, serum alkaline phosphatase and PTH were reduced to normal (Soliman et al., 2010). By three months, the vitamin D treatment improved leg bowing in two-thirds of the patients whereas 95% of the children had no radiological evidence of rickets. There were no instances of hypercalcemia, suggesting that this level of vitamin D supplementation was safe and effective for these vitamin D deficient children (Soliman et al., 2010). Results from a nationwide program in Turkey whose aim was to distribute free vitamin D drops to all newborns and infants (0–12 months) seen at primary health stations throughout the country showed that the prevalence of rickets dropped from 6% in 1998 to 0.1% in 2008 (Hatun et al., 2011).

The vitamin D status of the newborn is directly dependent on the mother's vitamin D status. Using monozygotic and dizygotic twin pairs, maternal serum 25(OH)D concentrations were found to be a significant factor in neonatal serum 25(OH)D concentrations, with limited effects of genetic factors (Novakovic et al., 2012). During lactation, maternal 25(OH)D status is correlated to 25(OH)D levels in breast milk ($r^2 = 0.48$) (Hollis et al., 1986). Thus, in exclusively breast-fed infants, breast milk can be a complete food but only if the mother has an adequate vitamin D status. Higher frequencies of rickets are observed in prolonged breast-fed children who are not given vitamin D supplementation (Brannon and Picciano, 2011). In a small study, vitamin D supplementation of fully breastfeeding mothers, but not their infants, for 3 months with 4000 IU or 2000 IU (100 μg or 50 μg) vitamin D per day was instituted to achieve optimal vitamin D status as denoted by the authors as 25(OH)D levels $\geq$ 80 nmol/l ($\geq$ 32 ng/ml). Mothers and infants in the 4000 IU/day group had higher 25(OH)D concentrations than the lower dose group, the average maternal 25(OH)D levels were higher than 80 nmol/l in both groups, infant 25OHD levels were 69.5 ± 9.75 nmol/l (27.8 ± 3.9 ng/ml) and 77 ± 12.5 nmol/l (30.8 ± 5.0 ng/ml) in the 4000 and 2000 IU/day groups respectively; neither group exhibited signs of vitamin D toxicity (Basile et al., 2006). In exclusively breast-fed infants in Finland, supplementation of the mother with 2000 IU (50 μg) per day for 15 weeks following delivery, or supplementation of the infant (but not the mother) with 400 IU (10 μg) per day for 15 weeks, resulted in similar infant vitamin D concentrations, indicating that infants can be supplemented directly or through the mother. Both of these infant groups had higher 25(OH)D concentrations than infants from mothers who were supplemented with 1000 IU (25 μg) per day during lactation (Ala-Houhala et al., 1986).

In a randomized, double-blind, placebo-controlled trial, supplementation of 400 IU (10 μg) per day of vitamin D during lactation did not markedly increase average circulating 25(OH)D concentrations in the mothers although at five of the seven visits, vitamin D levels were above the cutoff used for vitamin D sufficiency (≥75 nmol/L; ≥30 ng/ml) (Wagner et al., 2006). In contrast, mothers who received 6400 IU (160 μg) vitamin D per day, had a 73% increase in vitamin D concentrations after 6 months of supplementation compared to their baseline, and a dramatic increase in the antirachitic activity of their milk. Infants from mothers receiving the low dose supplement (400 IU/day) were given 300 IU (7.5 μg) per day in a liquid multivitamin preparation. These infants had similar 25(OH)D concentrations as infants who did not receive oral supplements but whose mothers received the high vitamin D dose (6400 IU/day); thus the vitamin D obtained through breast milk from high dose vitamin D-supplemented mothers was sufficient to maintain a vitamin D status similar to infants who directly received oral vitamin D supplements. No adverse effects were reported (Wagner et al., 2006). In a recent randomized controlled trial in the US, Hollis et al. administered vitamin D supplements of 400, 2000, or 4000 IU (10, 50, or 100 μg, respectively) per day from 12 to 16 weeks gestation through pregnancy with no side-effects or adverse events reported (Hollis et al., 2011). Vitamin D sufficiency was denoted as ≥80 nmol/l (≥ 32 ng/ml). Using this criterion, 82% of the women in the 4000 IU/day group achieved sufficiency at 1 month prior to delivery versus 73.9% and 50% of the women in the 2000 and 400 IU/day groups, respectively (Hollis et al., 2011). As assessed at birth, there was a significant effect of maternal vitamin D supplementation on infant 25(OH)D concentrations with the highest levels achieved in the 4000 IU/day supplemented group.

Using bone health as the criteria, in their 2011 report, the IOM recommended 600 IU/day (15 μg/day) for pregnancy and lactation (Institute of Medicine, 2011). For infants, the AI was set at 400 IU/day (10 μg/day). The American Academy of Pediatrics (2011) recommends that infants less than 6 months of age avoid direct sunlight exposure and wear protective clothing and hats, thus they recommend vitamin D supplementation of 400 IU (10 μg) per day for all breastfed and non-breastfed infants (American Academy of Pediatrics Council on Environmental Health, 2011). It is important to note that the above recommendation regarding the use of supplements questions the concept that one can get all of their nutrients in appropriate amounts through the simple consumption of a "good diet" (e.g., in this case, breast milk). Given that maternal vitamin D status directly affects breast milk vitamin D concentrations, if an infant will be exclusively breast fed, the mother must have sufficient vitamin D in breast milk to satisfy the infant's requirement, otherwise a vitamin D supplement is necessary to maintain adequate vitamin D status particularly in the infant with limited sunlight exposure.

A number of studies, both observational and randomized controlled trials, have investigated the effect of vitamin D supplementation on indices of fetal bone health. While some studies show a relationship between maternal vitamin D and bone mineral content of the infant, others do not (Brannon and Picciano, 2011; Liu and Hewison, 2011). Other outcomes that have been associated with low maternal vitamin D status or affected by vitamin D supplementation in some, but not all observational or randomized controlled trial studies, include low birthweight and small-for-gestational age (SGA) births (Gale et al., 2008; Bodnar and Simhan, 2010; Leffelaar et al., 2010; Thorne-Lyman and Fawzi, 2012). A recent meta-analysis of maternal vitamin D supplementation trials show a non-statistically significant 33% decrease in the risk for SGA (Thorne-Lyman and Fawzi, 2012) while a meta-analysis of maternal vitamin D levels showed that women with 25(OH)D concentrations <50 nmo/l (<20 ng/ml) had an increased risk of SGA (odds ratio 1.52; confidence intervals 1.08–2.14) (Wei et al., in press). After adjusting for confounders, Bodnar et al. reported a U-shaped risk relationship between serum 25(OH)D concentrations and SGA (defined as live-born infants <10th percentile of birth weight using a local population-based birthweight standard) in white, but not black women (Bodnar et al., 2010). The lowest risk of SGA occurred when maternal 25(OH)D concentrations were from 60 to 80 nmol/l (24–32 ng/ml). In white women, compared with serum 25(OH)D concentrations of 37.5 to 75 nmol/l (15–30 ng/ml), the SGA odds ratio for 25(OH)D concentrations <37.5 nmol/l was 7.5 and odds ratio for SGA for 25(OH)D concentrations >75 nmol/l was 2.1. In addition, different SNPs in the VDR gene were associated with SGA among white versus black women suggesting that differences in genetic polymorphisms as well as metabolism affect the relationship between vitamin D and fetal growth (Bodnar et al., 2010). Using a large sample size (2,146 term infants) from the Collaborative Perinatal Project conducted from 1959 to 1965 in the US, Gernand et al. recently reported that first trimester maternal serum 25(OH)D concentrations ≥ 37.5 nmol/l (≥ 15 ng/ml) was associated with nearly a 50% reduction in the risk of SGA (Gernand et al., 2013). The relationships between maternal 25(OH)D and infant birth weight and head circumference were positive and linear up to 37.5 nmol/l after which they leveled off (Gernand et al., 2013).

A recent review indicates that no teratogenic effects of maternal vitamin D supplementation in humans have been noted (Roth, 2011). The highest doses are reported for women with hypoparathyroidism who were treated with vitamin D2 (50,000–200,000 IU vitamin D2/day). In these cases,

there were no adverse effects reported in their infants (Goodenday and Gordon, 1971; Bolen, 1973). In a review of vitamin D clinical trials, no toxicity was noted when supplements of 10,000 IU (250 μg) per day were given (Hathcock et al., 2007). However, in experimental animal studies, high dose vitamin D administration (26–90 mg/kg) has been reported to result in impaired fetal growth and osteogenesis, increased placental damage, and mortality (Tshibangu et al., 1975; Chan et al., 1979; Ariyuki, 1987; Roth, 2011), although maternal toxicity may have accounted for some of the effects.

CHILD

In addition to rickets, other clinical symptoms of vitamin D deficiency in children have been noted. In a retrospective survey of children reported to be vitamin D insufficient (<50 nmol/l; <20 ng/ml) in the United Kingdom, abdominal pain was the most common clinical feature (19%), with seizures and limb pain affecting around 16% of the children (Kehler et al., 2012). In Scotland, 160 cases of symptomatic vitamin D deficiency affecting infants and children aged 2 weeks to 14 years were identified between 2002 and 2008 (Ahmed et al., 2011). Forty percent of the children had bowed legs and 12% were characterized as having had a fit (Ahmed et al., 2011). Thus, atypical musculoskeletal pain can accompany vitamin D deficiency (Clarke and Page, 2012). Infants diagnosed with rickets exhibited cardiomyopathy characterized by an increased ratio of interventricular septal thickness to left ventricular posterior wall thickness which was normalized after oral treatment with vitamin D (200,000 IU/day, three times a day) and calcium lactate (1 g/day) for 2 weeks (Uysal et al., 1999).

Intrauterine as well as early postnatal nutrition can impact development and have long-lasting consequences. Infants from mothers with low vitamin D status had lower tibia bone mineral content (BMC) at birth (Viljakainen et al., 2010, 2011) but by 14 months, BMC was not different than in infants from mothers with high vitamin D status (Viljakainen et al., 2011). However, lower tibial total bone cross-sectional area persisted in the infants from low vitamin D mothers despite postnatal vitamin D supplementation (Viljakainen et al., 2011). Postnatal vitamin D supplementation of the infant only partly ameliorated the altered bone growth induced by prenatal vitamin D insufficiency, thus longer-term and possibly persistent consequences of prenatal vitamin D status should be considered. Meta-analysis of six placebo-controlled RCTs of vitamin D supplementation of at least 3 months duration in children showed no effects of supplementation on BMC (total body) or bone mineral density (BMD) of hip or forearm (Winzenberg et al., 2010). However, in the children with low serum vitamin D status, vitamin D supplementation increased total BMC and lumbar spine BMD suggesting that supplementation of vitamin D to targeted populations can be beneficial.

Vitamin D has been shown to inhibit adaptive immunity and enhance innate immunity (Di Rosa et al., 2011). The innate immune system is a rapid, first line of host defense to infection with nonspecific recognition of common microbial patterns and structures. Vitamin D insufficiency has been reported to increase the risk for infections such as tuberculosis, pneumonia, acute lower respiratory tract infections as well as the common cold (Walker et al., 2011). There are a number of mechanisms that might underlie the impact of vitamin D on the immune system. Liu et al. reported that Toll-like receptor (TLR) activation increased antimicrobial cathelicidin production via upregulation of VDR and 1-α-hydroxylase (CYP27B1) genes leading to the killing of *Mycobacterium tuberculosis* (Liu et al., 2006). Monocytes incubated with sera from African-American individuals that were characterized by low vitamin D concentrations, resulted in low TLR-induced cathelicidin induction which was increased with exogenous 25(OH)D supplementation (Liu et al., 2006). Cod liver oil and photo-therapy has been used historically to treat tuberculosis (Arora and Hobel, 2010). Clinical trials of vitamin D supplementation to patients with active tuberculosis infection have not shown major benefits overall although larger trials with perhaps higher doses that control for confounders are needed (Ralph et al., 2013). Inappropriate innate immune system response can result in sepsis in the newborn. Monocytes cultured in vitamin D-deficient plasma from term newborns (25(OH)D <30 nmol/l; <12 ng/ml) had lower cathelicidin expression in response to stimulation by ligands for TLR4 and TLR2/1 compared to monocytes cultured in cord blood with 25(OH)D concentrations >75 nmol/l (>30 ng/ml) (Walker et al., 2011). When the vitamin D-deficient plasma was supplemented with 25(OH)D, monocyte-induced antimicrobial peptide gene expression was increased, suggesting that the ability of the immune cells to respond to a pathogenic challenge can be functionally affected by vitamin D concentrations (Walker et al., 2011). The innate immune response is particularly important in neonates whose acquired T- and B-cell response to infections is less developed than adults (Walker et al., 2011).

Low cord blood 25(OH)D concentrations in neonates have also been associated with an increased risk of respiratory syncytial viral bronchiolitis in the first year of life (Belderbos et al., 2011). Numerous studies report associations between low vitamin D intake or low 25(OH)D concentrations with an increased risk of respiratory infection, wheezing and asthma (Erkkola et al., 2009; Brehm et al., 2010; Carroll et al., 2011; Di Rosa et al., 2011; Hollis and Wagner, 2011). Asthma exacerbations are commonly precipitated by respiratory tract infections. In a randomized, double-blind, placebo-controlled trial, children receiving 1200 IU (30 μg) per day of vitamin D during the winter had a lower incidence of

influenza A (Urashima et al., 2010). Sabetta et al. (2010) reported that maintenance of 25(OH)D concentrations of 95 nmol/l (38 ng/ml) or higher is associated with significantly reduced incidence of acute viral respiratory tract infections during the fall and winter in temperate zones. The IOM and Endocrine Society's Clinical Practice Guideline recommendation for children at least 1 year of age is 600 IU per day and 600 to 1000 IU per day, respectively.

Vitamin D has been reported to reduce adaptive immunity in part by decreasing pro-inflammatory cytokines, and inhibiting T-cell proliferation (Reinholz et al., 2011). A number of observational studies have investigated the relationship between maternal vitamin D dietary intake and risk for asthma or asthma morbidity in their children (Paul et al., 2012) with the thought that predisposition to allergies may already be acquired in utero. After adjusting for potential confounders, the highest compared to the lowest quintiles of maternal vitamin D intake at 32 weeks of gestation was associated with a lower risk for wheeze and decreased bronchodilator response in the children at 5 years of age (Devereux et al., 2007). A similar association between higher maternal vitamin D intake and a lower risk of recurrent wheeze in children by age 3 years was reported by Camargo et al. (2007). In a meta-analysis, high maternal dietary vitamin D (and E) intakes were associated with a decreased development of wheezing outcomes (Nurmatov et al., 2011). Vitamin D insufficiency was also associated with a higher risk of severe asthma exacerbations in Puerto Rican children (Brehm et al., 2012). In animals, maternal vitamin D deficiency resulted in decreased lung distensibility (Gaultier et al., 1984) and reduced lung volume and number of alveoli in offspring (Zosky et al., 2011) compared to vitamin D adequate controls, indicating that vitamin D plays a role in lung development, maturation, and function. While some studies have shown an association between low vitamin D and asthma, Hughes et al. report that cod liver oil supplementation before age 15 is associated with an increased risk of asthma and hay fever (Hughes et al., 2011). Very low or very high 25(OH)D levels have been associated with elevated IgE levels (Hypponen et al., 2009). Some studies have shown that maternal 25(OH)D concentrations in pregnancy $>$75 nmol/l ($>$ 30 ng/ml) or vitamin D supplementation in children were associated with increased risk of developing atopic eczema or allergic asthma (Gale et al., 2008; Reinholz et al., 2011). Recently, a higher risk of developing food allergy by 2 years of age was observed in children who had higher cord blood 25(OH)D concentrations or whose mothers had higher 25(OH)D levels (Weisse et al., 2013). Together, these studies suggest there may be negative as well as beneficial effects of vitamin D; thus the issue of vitamin D and allergic sensitization is complex and clearly merits further study.

VITAMIN D AND RISK OF CHRONIC DISEASE

With regard to CVD, low vitamin D levels have been associated with several risk factors for CVD, including obesity, diabetes, hypertension, altered lipid profiles, and endothelial dysfunction. In a meta-analysis, an inverse association was found between CVD risk and 25(OH)D concentrations from 20 to 60 nmol/l (8–24 ng/ml) (Wang et al., 2012). A recent report from the Ludwigshafen Risk and Cardiovascular Health (LURIC) study shows that after adjusting for confounders, vitamin D deficiency (defined as $<$25 nmol/l ($<$10 ng/ml)) was associated with a higher all-cause and CVD mortality compared with those who had optimal vitamin D concentrations (Thomas et al., 2012). Concentrations of 25(OH)D have also been inversely associated with systolic blood pressure and plasma glucose levels in US adolescents, independent of adiposity (Reis et al., 2009). In a randomized, blinded, controlled clinical trial, black boys and girls were randomized to receive 400 IU/day (controls) or 2000 IU/day (supplemented). Results showed that aortic stiffness (measured by pulse wave velocity) was reduced in the 2000 IU/day vitamin supplemented group (Dong et al., 2010). Harris et al. (2011) showed that 16 weeks of vitamin D supplementation (2000 IU/day) improved flow-mediated dilation in overweight African American adults while vitamin D insufficiency was reported to be associated with lower coronary flow reserve in men (Karohl et al., 2012). Using a rodent model, Tare et al. fed rat dams a vitamin D deficient or adequate diet prior to and during pregnancy and lactation. The offspring were fed the same diets as the dams for 7 to 8 weeks. Results showed that the offspring who had in utero and early life exposure to vitamin D deficient diets had markedly elevated blood pressures and heart rates than offspring fed a vitamin D adequate diet (Tare et al., 2011). This adverse cardiovascular phenotype was characterized by abnormal endothelium-dependent relaxation (likely mediated by NO) in males and dioestrous females. At four weeks of age, offspring of vitamin D-deficient rat dams had an increase in left ventricular volume compared to vitamin D adequate offspring which is consistent with other studies showing that cardiac morphology can be altered with prenatal vitamin D deficiency (Gezmish et al., 2010).

A number of studies have investigated the relationship between vitamin D and multiple sclerosis, an inflammatory disease of the central nervous system characterized by demyelination and oligodendrocyte, axonal and neuronal injury, and loss. Willer et al. reported that the timing of birth (which can impact vitamin D endogenous production) increased the risk of multiple sclerosis for people born in May (Willer et al., 2005). Meta-analysis of over 78,000 patients with multiple sclerosis showed a significant excess of multiple sclerosis risk for those born in April and a reduction in risk

for those born in October and November (Dobson et al., 2013). When only data from studies performed at latitudes less than 52°N were analyzed, there was no effect of month of birth on multiple sclerosis risk indicating that the UV variation over the course of a year in lower latitude studies had less effect than in those studies performed at $>52°$N, where insufficient UV light of the wavelength that could enable vitamin D synthesis reaches the skin between October and March (Dobson et al., 2013). Polymorphism in the vitamin D metabolizing gene (CYP27B1) has been associated with an increased risk of multiple sclerosis (Ramagopalan et al., 2011). Investigators have also reported that multiple sclerosis patients have lower vitamin D levels with associative lower BMD and higher rates of disability (Koch et al., 2013). It is hypothesized that vitamin D-induced changes in the immune system may contribute to neuroprotection (Koch et al., 2013).

Type I diabetes mellitus is also classified as having an immune-mediated component and like multiple sclerosis, vitamin D may affect the incidence of diabetes. Hypponen et al. reported that infants who consumed vitamin D supplements irrespective of dose, (recommended dose; 2000 IU daily) during their first year of life, had a reduced risk of developing diabetes compared to infants who did not receive supplements (median age of diabetes diagnosis was 14 years) (Hypponen et al., 2001). It has been postulated that the immunosuppressive properties of vitamin D may inhibit autoimmune destruction of β cells of the pancreas. Animal studies have reported that administration of a 1,25(OH)2D analog inhibited the Th1 response and reduced the incidence of autoimmune diabetes in NOD mice (Gregori et al., 2002). In humans, genetic VDR polymorphisms have been associated with increased susceptibility of type I diabetes (Pani et al., 2000).

In addition to multiple sclerosis and diabetes, prenatal or early postnatal vitamin D deficiency may affect disorders with a developmental basis such as schizophrenia. In rodent models, vitamin D deficiency during pregnancy results in abnormal brain development and neuropsychiatric behavior in the offspring (O'Loan et al., 2007; Harms et al., 2008; Eyles et al., 2011). Maternal vitamin D deficiency decreases the expression of factors involved in dopaminergic neuron development in the rat fetal brain (Cui et al., 2010). The VDR has recently been found in dopaminergic neurons in substantia nigra in humans as well as in rat embryos early in development (Cui et al., 2013). There is growing evidence of a link between schizophrenia and low vitamin D in humans (McGrath et al., 2010). Male infants who had received vitamin D supplements during their first year of life had a reduced risk of schizophrenia by age 31 years (McGrath et al., 2004). The incidence of schizophrenia appears to follow a latitudinal gradient with higher rates observed in northern latitudes. Using genotype data (660,000 SNPs loci), Amato et al. reported that latitude-related genes also characterized genes associated with schizophrenia and there was a significant overlap of genes between schizophrenia and vitamin D-related genes (Amato et al., 2010). An increased risk for schizophrenia has been reported in black immigrants who have migrated, compared to the native population (Dealberto, 2010). Whether the link connecting schizophrenia and latitude is vitamin D merits further study. In most studies, higher rates of schizophrenia are observed in black versus white populations in the US (Dealberto, 2010).

Vitamin D can protect against a number of experimental autoimmune diseases in animals including autoimmune encephalomyelitis and systemic lupus (Christakos and DeLuca, 2011). Autism, a neurodevelopmental disorder characterized by impaired social interaction, verbal/nonverbal communication, and repetitive and stereotyped behavioral patterns, has been speculated to have an autoimmune component in a subset of patients (Mostafa and Al-Ayadhi, 2012). Children with autism had lower vitamin D status, which was associated with higher levels of anti-myelin-associated glycoprotein (anti-MAG) antibodies, and vitamin D concentrations were negatively associated with autism symptoms (Mostafa and Al-Ayadhi, 2012). As with schizophrenia, maternal immigrant status is associated with an increased risk of autism (Dealberto, 2011). Further studies are needed to determine whether the observed associations are causal in nature.

LONG-TERM EFFECTS—EPIGENETICS

Potential epigenetic mechanisms have been suggested to underlie some of the beneficial effects of vitamin D that may be important in altering the risk of chronic diseases later in life (Hossein-nezhad and Holick, 2012). Activation of the VDR has been shown to modify histone acetyl transferase activity, which can influence gene transcription and repression (Hossein-nezhad and Holick, 2012). Pereira et al. have reported that 1,25(OH)2D activation of the VDR induces the transcription of genes encoding for certain histone demethylases that may contribute to epigenetic regulation (Pereira et al., 2012). It has also been speculated that vitamin D-induced interactions with histone acetyltransferases and histone deacetylases can modify chromatin and mediate epigenetic events on genes involved in susceptibility for chronic lung disease (Sundar and Rahman, 2011).

Using a genome-wide methylation scan, Zhu et al. analyzed leukocyte DNA methylation between vitamin D deficient (defined as 25(OH)D $\leq$ 25 nmol/l or $\leq$ 10 ng/ml) and age-matched African American adolescent controls (defined as 25(OH)D $>$ 75 nmol/l or $>$30 ng/ml). A number of genes were identified whose methylation levels were significantly enriched in the vitamin D deficient group (Zhu et al., in press). These included DHCR7 (7-dehydrocholesterol reductase enzyme), CYP2R1 (hepatic microsomal enzyme 25-hydroxylase), and CYP24A1 (24-

hydroxylase), all of which are involved in vitamin D metabolism. What remains to be elucidated is whether the methylation changes are the cause or the consequence of vitamin D deficiency. The largest difference in methylation levels was noted for the MAPRE2 gene (methylation levels 37% lower in vitamin D deficient leukocytes than controls). The MAPRE2 gene encodes microtubule-associated proteins involved in processes such as cell division and migration, processes important to the cancer process. Hypermethylation of the DIO3 gene, involved in thyroid axis function, occurred in the vitamin D deficient group. Hematological tumors also present with higher methylation status of this gene (Zhu et al., in press). Gene ontology analysis indicated that the differentially methylated genes in the low vitamin D group resulted in an enriched molecular function for Wnt binding protein. Others have reported that VDR deficiency induced in vitro by shRNA knock-down of VDR expression in human colon cancer cells, or induced in vivo by generating $Apc^{min/+}$ mice that were also VDR-null, enhances Wnt/β-catenin signaling, which can contribute to the initiation and progression of colon cancer (Larriba et al., 2011). In colorectal cancer patients, low vitamin D intake has been associated with higher levels of methylation in the promoter of the DKK1 gene, a Wnt suppressor protein with antiproliferative and proapoptotic properties, compared to high vitamin D intake (Rawson et al., 2012). Hypermethylation silences DKK1, allowing Wnt signaling to increase, which can contribute to cell proliferation.

VITAMIN D TOXICITY

As with all essential nutrients, vitamin D intake and concentrations in blood have been noted to have a U- or J-shaped curve with regard to adverse effects due to deficiency and toxicity. While it is unusual to see vitamin D toxicity from dietary intake of food, high dose administration of vitamin D can result in toxicity signs. For example, elderly patients in India who received very high intramuscular doses of vitamin D (600,000 U/injection; duration ranged from 5 weeks to 3 years) had average serum 25(OH)D concentrations of 325.6 ± 55.0 nmol/l (130.23 ± 21.98 ng/ml) (Pandita et al., 2012). These patients were characterized with hypercalcemia and vague non-specific symptoms included dehydration, fatigue, generalized body weakness, altered sensorium, anorexia, polyuria and polydipsia, constipation, and vomiting. The IOM reports that there may be reason for concern at serum 25(OH)D concentrations above 125 nmol/l (50 ng/ml). Individuals with high sun exposure such as lifeguards have been reported to have 25(OH)D concentrations greater than 150 nmol/l (60 ng/ml) (Vieth, 1999).

Supraphysiological doses of vitamin D, e.g. annual injection of 300,000 IU (7500 μg) vitamin D2 over 3 years have been associated with an increased risk of hip/femur and hip/femur/wrist fracture in elderly women (Sanders et al., 2013). In another randomized controlled trial, annual oral doses of 500,000 IU (12,500 μg) vitamin D3 increased the rate of falls and fractures in elderly women (Sanders et al., 2013). There has been some discussion that vitamin D has steroid-like effects and may have enabled the vitamin D-supplemented elderly women to feel better, have less pain, and be more mobile; however, their coordination might have lagged behind the improved muscle function and contributed to a greater number of falls (Kupferschmidt, 2012). In both of these randomized controlled trials, the results call into question the safety of supra-high loading doses of vitamin D.

In a recent study, 25(OH)D concentrations were negatively associated with CRP, an inflammatory marker; however, vitamin D concentrations above 50 nmol/l (20 ng/ml) were also associated with increased CRP (Amer and Qayyum, 2012). These data suggest that vitamin D supplementation might help reduce inflammation in those individuals with low serum vitamin D. Future studies should assess the vitamin D status of the subjects before, during, and after treatment to determine whether vitamin D supplementation to vitamin D-replete individuals can increase the risk of adverse events. This has been observed when pregnant women already in good iron status are supplemented with iron. Indiscriminate iron supplementation has been reported to increase the risk for maternal hypertension and increase the incidence of SGA infants (Ziaei et al., 2007).

SUMMARY AND CONCLUSION

Research in the broad area of vitamin D and health has seen significant growth in the last several years. The renewed interest in vitamin D has been fueled in part by the observation that the occurrence of childhood rickets in developed countries, which was at one time largely eradicated through the use of vitamin D-fortified foods, appears to be on the rise. The reasons for the reemergence of rickets are complex, but are thought to include reductions in the consumption of vitamin D-fortified foods and reductions in the exposure of many individuals to sunlight. Ironically, the above potential causes of suboptimal vitamin D status are in part the result of actions taken by individuals in an effort to improve their health, e.g. reducing sun exposure, decreasing intake of milk, eggs, margarine. This is similar to the current report of low iodine status in some population groups (Obican et al., 2012) as a result of individuals reducing table salt intake, which is viewed as a positive health action. Clearly, the apparent increasing incidence of childhood rickets indicates a continuing need for public health education, and public health measures aimed at preventing this childhood disease, and suboptimal vitamin D status, in general.

In addition to the above, at present there are numerous outstanding questions concerning the role of vitamin D in the optimization of maternal and fetal health. There is increasing evidence that in addition to bone health, vitamin D plays a

critical function in the regulation of the immune system (e.g., see Selgrade et al., this volume), and it is important for vascular health due to its ability to influence endothelial function. It has been argued that given these newly appreciated functions of vitamin D, a re-evaluation of the dietary recommendations for vitamin D is in order. What are needed are the metabolic details of how maternal vitamin D supplementation affects fetal metabolism and health. Additionally, it is important to establish the window of safety for high dose vitamin D during different gestational ages of pregnancy in fair-skinned and dark-skinned populations. When determining the optimal level of vitamin D intake during pregnancy, one must consider both the health of the mother as well as the fetus. If supplementation is recommended, what doses, frequencies, and routes are the safest and most effective? Do these recommendations change depending on the trimester of pregnancy? Depending on the season? Depending on skin color? Brembeck et al. (2013) recently reported that vitamin D insufficiency defined as 25(OH)D concentration < 50 nmol/l (<20 ng/ml) and vitamin D deficiency defined as 25(OH)D concentrations < 30 nmol/l (<12 ng/ml) affects 65% and 17% of fair-skinned pregnant women living in Sweden, respectively. In winter, these rates increased to 85% and 28%, respectively. Should vitamin D status be assessed before entry into a clinical trial and should supplementation be targeted to at-risk populations? Numerous risk factors for low vitamin D are known (Fig. 1). How does supplementation affect serum concentrations of 25(OH)D (pharmacokinetics) and can serum levels be used as a predictor of disease risk?

In addition to monitoring indices of calcium metabolism, other parameters affected by vitamin D status including blood pressure and heart function should be assessed. Moreover, are there teratogenic effects that can be attributed to excessive maternal vitamin D supplementation? Trained neonatologists and teratologists can contribute to this endeavor. It is worth noting that in many regards, current debates regarding vitamin D supplements during pregnancy are similar to those in the past concerning folate; requirements may be influenced by relatively common polymorphisms, there are large segments of the population that may be characterized by low vitamin D status even if they consume a "good diet" and finally, there may be a plethora of negative maternal and fetal affects associated with marginal deficiencies. The epigenetic consequences of high vitamin D exposures also merit attention, particularly with respect to immune and cardiovascular functions. An additional approach that may be useful in the future is the creation of statistical models to predict serum 25(OH)D concentrations. As an example, Bjorn Jensen et al. have created a predictive model specific to mid-pregnancy which includes vitamin D intake (diet and supplements), outdoor physical activity, tanning bed use, smoking, and month of blood draw. Their predictive model explained 40.1% of the variance in measured 25(OH)D (data from the Danish National Birth Cohort; $N = 1{,}494$) and suggested that it could be used to rank individuals in order to relate predicted vitamin D status to health outcomes (Bjorn Jensen et al., 2013). While predictive models may be useful when vitamin D biomarker assessment is not possible, well-designed, adequately-powered, well-executed randomized clinical trials that sufficiently control for confounding factors and are long enough in duration to determine long-term effects are needed to address many of the issues above.

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REFERENCES

Adams JS, Hewison M. 2012. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Arch Biochem Biophys 523:95–102.

Agarwal N, Arya SC. 2011. Vitamin D levels in pregnant women and newborns at a private tertiary care hospital in Delhi, India. Int J Gynaecol Obstet 113:240–241.

Ahmed SF, Franey C, McDevitt H, et al. 2011. Recent trends and clinical features of childhood vitamin D deficiency presenting to a children's hospital in Glasgow. Arch Dis Child 96:694–696.

Ala-Houhala M, Koskinen T, Terho A, et al. 1986. Maternal compared with infant vitamin D supplementation. Arch Dis Child 61:1159–1163.

Amato R, Pinelli M, Monticelli A, et al. 2010. Schizophrenia and vitamin D related genes could have been subject to latitude-driven adaptation. BMC Evol Biol 10:351.

Amer M, Qayyum R. 2012. Relation between serum 25-hydroxyvitamin D and C-reactive protein in asymptomatic adults (from the continuous National Health and Nutrition Examination Survey 2001 to 2006). Am J Cardiol 109:226–230.

American Academy of Pediatrics Council on Environmental Health. 2011. Ultraviolet radiation: a hazard to children and adolescents. Pediatrics 127:588–597.

Andersen L, Abrahamsen B, Dalgård C, Kyhl H, Beck-Nielsen S, Frost-Nielsen M, Jørgensen J, Barington T, Christesen H. Parity and tanned white skin as novel predictors of vitamin D status in early pregnancy: a population-based cohort study. Clin Endocrinol (Oxf) 2013. doi: 10.1111/cen.12147. [Epub ahead of print].

Andraweera PH, Dekker GA, Laurence JA, et al. 2012. Placental expression of VEGF family mRNA in adverse pregnancy outcomes. Placenta 33:467–472.

Ariyuki F. 1987. Growth retardation induced in rat fetuses by maternal fasting and massive doses of ergocalciferol. J Nutr 117:342–348.

Arora CP, Hobel CJ. 2010. Vitamin D—a novel role in pregnancy. Biopolymers and Cell 26:1–8.

Bang UC, Semb S, Nordgaard-Lassen I, et al. 2009. A descriptive cross-sectional study of the prevalence of 25-hydroxyvitamin D deficiency and association with bone markers in a hospitalized population. Nutr Res 29:671–675.

Barger-Lux MJ, Heaney RP. 2002. Effects of above average summer sun exposure on serum 25-hydroxyvitamin D and calcium absorption. J Clin Endocrinol Metab 87:4952–4956.

Barrera D, Avila E, Hernandez G, et al. 2008. Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. Reprod Biol Endocrinol 6:3.
Basile LA, Taylor SN, Wagner CL, et al. 2006. 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 1:27–35.
Belderbos ME, Houben ML, Wilbrink B, et al. 2011. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics 127:e1513–1520.
Bjorn Jensen C, Thorne-Lyman AL, Vadgard Hansen L, et al. 2013. Development and validation of a vitamin D status prediction model in Danish pregnant women: a study of the Danish National Birth Cohort. PLoS One 8:e53059.
Blumfield ML, Hure AJ, Macdonald-Wicks L, et al. 2013. A systematic review and meta-analysis of micronutrient intakes during pregnancy in developed countries. Nutr Rev 71:118–132.
Bodnar LM, Catov JM, Simhan HN, et al. 2007a. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab 92:3517–3522.
Bodnar LM, Catov JM, Zmuda JM, et al. 2010. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. J Nutr 140:999–1006.
Bodnar LM, Krohn MA, Simhan HN. 2009. Maternal vitamin D deficiency is associated with bacterial vaginosis in the first trimester of pregnancy. J Nutr 139:1157–1161.
Bodnar LM, Simhan HN. 2010. Vitamin D may be a link to black-white disparities in adverse birth outcomes. Obstet Gynecol Surv 65:273–284.
Bodnar LM, Simhan HN, Powers RW, et al. 2007b. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr 137:447–452.
Bolen JW. 1973. Hypoparathyroidism in pregnancy. Am J Obstet Gynecol 117:178–179.
Brannon PM, Picciano MF. 2011. Vitamin D in pregnancy and lactation in humans. Annu Rev Nutr 31:89–115.
Brannon PM, Yetley EA, Bailey RL, et al. 2008. Overview of the conference "Vitamin D and Health in the 21st Century: an Update". Am J Clin Nutr 88:483S–490S.
Brehm JM, Acosta-Perez E, Klei L, et al. 2012. Vitamin D insufficiency and severe asthma exacerbations in Puerto Rican children. Am J Respir Crit Care Med 186:140–146.
Brehm JM, Schuemann B, Fuhlbrigge AL, et al. 2010. Serum vitamin D levels and severe asthma exacerbations in the Childhood Asthma Management Program study. J Allergy Clin Immunol 126:52–58.
Brembeck P, Winkvist A, Olausson H. 2013. Determinants of vitamin D status in pregnant fair-skinned women in Sweden. Br J Nutr 1–9.
Bu FX, Armas L, Lappe J, et al. 2010. Comprehensive association analysis of nine candidate genes with serum 25-hydroxy vitamin D levels among healthy Caucasian subjects. Hum Genet 128:549–556.
Calvo MS, Whiting SJ, Barton CN. 2004. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr 80:1710S–1716S.
Camadoo L, Tibbott R, Isaza F. 2007. Maternal vitamin D deficiency associated with neonatal hypocalcaemic convulsions. Nutr J 6:23–24.
Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, et al. 2007. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr 85:788–795.
Cardus A, Panizo S, Encinas M, et al. 2009. 1,25-dihydroxyvitamin D3 regulates VEGF production through a vitamin D response element in the VEGF promoter. Atherosclerosis 204:85–89.
Carlson CR, Uriu-Adams JY, Chambers CD, et al. 2012. Low Vitamin D status is a common finding in a population of pregnant women enrolled in a nutrition intervention study in the Ukraine. FASEB J 26:lb281.
Carroll KN, Gebretsadik T, Larkin EK, et al. 2011. Relationship of maternal vitamin D level with maternal and infant respiratory disease. Am J Obstet Gynecol 205:215 e211–215 e217.
Chan GM, Buchino JJ, Mehlhorn D, et al. 1979. Effect of vitamin D on pregnant rabbits and their offspring. Pediatr Res 13:121–126.
Chesney RW. 2012. Theobald Palm and his remarkable observation: how the sunshine vitamin came to be recognized. Nutrients 4:42–51.
Chesney RW, Hedberg G. 2010. Metabolic bone disease in lion cubs at the London Zoo in 1889: the original animal model of rickets. J Biomed Sci 17 (Suppl 1):S36–S39.
Christakos S, DeLuca HF. 2011. Minireview: vitamin D: is there a role in extraskeletal health? Endocrinology 152:2930–2936.
Clarke NM, Page JE. 2012. Vitamin D deficiency: a paediatric orthopaedic perspective. Curr Opin Pediatr 24: 46–49.
Crozier SR, Harvey NC, Inskip HM, et al. 2012. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. Am J Clin Nutr 96:57–63.
Cui X, Pelekanos M, Burne TH, et al. 2010. Maternal vitamin D deficiency alters the expression of genes involved in dopamine specification in the developing rat mesencephalon. Neurosci Lett 486:220–223.
Cui X, Pelekanos M, Liu PY, et al. 2013. The vitamin D receptor in dopamine neurons; its presence in human substantia nigra and its ontogenesis in rat midbrain. Neuroscience 236:77–87.
Dealberto MJ. 2010. Ethnic origin and increased risk for schizophrenia in immigrants to countries of recent and longstanding immigration. Acta Psychiatr Scand 121:325–339.
Dealberto MJ. 2011. Prevalence of autism according to maternal immigrant status and ethnic origin. Acta Psychiatr Scand 123:339–348.
Devereux G, Litonjua AA, Turner SW, et al. 2007. Maternal vitamin D intake during pregnancy and early childhood wheezing. Am J Clin Nutr 85:853–859.
Di Rosa M, Malaguarnera M, Nicoletti F, et al. 2011. Vitamin D3: a helpful immuno-modulator. Immunology 134:123–139.
Diaz L, Arranz C, Avila E, et al. 2002. Expression and activity of 25-hydroxyvitamin D-1 alpha-hydroxylase are restricted in cultures of human syncytiotrophoblast cells from preeclamptic pregnancies. J Clin Endocrinol Metab 87:3876–3882.
Ding C, Gao D, Wilding J, et al. 2012. Vitamin D signalling in adipose tissue. Br J Nutr 108:1915–1923.
Dobson R, Giovannoni G, Ramagopalan S. 2013. The month of birth effect in multiple sclerosis: systematic review, meta-analysis and effect of latitude. J Neurol Neurosurg Psychiatry 84:427–432.
Dong J, Wong SL, Lau CW, et al. 2012. Calcitriol protects renovascular function in hypertension by down-regulating angiotensin II type 1 receptors and reducing oxidative stress. Eur Heart J 33:2980–2990.
Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. 2010. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. J Clin Endocrinol Metab 95:4584–4591.
Dror DK, Allen LH. 2010. Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions. Nutr Rev 68:465–477.
Dror DK, King JC, Durand DJ, et al. 2011. Association of modifiable and nonmodifiable factors with vitamin D status in pregnant women and neonates in Oakland, CA. J Am Diet Assoc 111:111–116.
Dusso AS, Brown AJ, Slatopolsky E. 2005. Vitamin D. Am J Physiol Renal Physiol 289:F8–F28.
Erkkola M, Kaila M, Nwaru BI, et al. 2009. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clin Exp Allergy 39:875–882.
Erten S, Kucuksahin O, Sahin A, et al. 2013. Decreased plasma vitamin D levels in patients with undifferentiated spondyloarthritis and ankylosing spondylitis. Intern Med 52:339–344.
Evans KN, Bulmer JN, Kilby MD, et al. 2004. Vitamin D and placental-

decidual function. J Soc Gynecol Investig 11:263–271.
Eyles D, Burne T, McGrath J. 2011. Vitamin D in fetal brain development. Semin Cell Dev Biol 22:629–636.
Gale CR, Robinson SM, Harvey NC, et al. 2008. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr 62:68–77.
Garg S, Sabri D, Kanji J, et al. 2013. Evaluation of vitamin D medicines and dietary supplements and the physicochemical analysis of selected formulations. J Nutr Health Aging 17:158–161.
Gaultier C, Harf A, Balmain N, et al. 1984. Lung mechanics in rachitic rats. Am Rev Respir Dis 130:1108–1110.
Gernand AD, Simhan HN, Klebanoff MA, et al. 2013. Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. J Clin Endocrinol Metab 98:398–404.
Gezmish O, Tare M, Parkington HC, et al. 2010. Maternal vitamin D deficiency leads to cardiac hypertrophy in rat offspring. Reprod Sci 17:168–176.
Giguere Y, Charland M, Theriault S, et al. 2012. Linking preeclampsia and cardiovascular disease later in life. Clin Chem Lab Med 50:985–993.
Goodenday LS, Gordon GS. 1971. No risk from vitamin D in pregnancy. Ann Intern Med 75:807–808.
Gordon NP, Caan BJ, Asgari MM. 2012. Variation in vitamin D supplementation among adults in a multi-race/ethnic health plan population, 2008. Nutr J 11:104.
Greer FR. 2008. 25-Hydroxyvitamin D: functional outcomes in infants and young children. Am J Clin Nutr 88:529S–533S.
Gregori S, Giarratana N, Smiroldo S, et al. 2002. A 1alpha,25-dihydroxyvitamin D(3) analog enhances regulatory T-cells and arrests autoimmune diabetes in NOD mice. Diabetes 51:1367–1374.
Grundmann M, Haidar M, Placzko S, et al. 2012. Vitamin D improves the angiogenic properties of endothelial progenitor cells. Am J Physiol Cell Physiol 303:C954–C962.
Halicioglu O, Aksit S, Koc F, et al. 2012. Vitamin D deficiency in pregnant women and their neonates in spring time in western Turkey. Paediatr Perinat Epidemiol 26:53–60.
Hamilton SA, McNeil R, Hollis BW, et al. 2010. Profound vitamin D deficiency in a diverse group of women during pregnancy living in a sun-rich environment at latitude 32 degrees N. Int J Endocrinol 2010:917428.
Hanson C, Armas L, Lyden E, et al. 2011. Vitamin D status and associations in newborn formula-fed infants during initial hospitalization. J Am Diet Assoc 111:1836–1843.
Harms LR, Eyles DW, McGrath JJ, et al. 2008. Developmental vitamin D deficiency alters adult behaviour in 129/SvJ and C57BL/6J mice. Behav Brain Res 187:343–350.
Harris RA, Pedersen-White J, Guo DH, et al. 2011. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. Am J Hypertens 24:557–562.
Harris SS. 2006. Vitamin D and African Americans. J Nutr 136: 1126–1129.
Hathcock JN, Shao A, Vieth R, et al. 2007. Risk assessment for vitamin D. Am J Clin Nutr 85:6–18.
Hatun S, Islam O, Cizmecioglu F, et al. 2005. Subclinical vitamin D deficiency is increased in adolescent girls who wear concealing clothing. J Nutr 135:218–222.
Hatun S, Ozkan B, Bereket A. 2011. Vitamin D deficiency and prevention: Turkish experience. Acta Paediatr 100:1195–1199.
Haugen M, Brantsaeter AL, Trogstad L, et al. 2009. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology 20:720–726.
Hensel KJ, Randis TM, Gelber SE, et al. 2011. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. Am J Obstet Gynecol 204: 41.e41–49.
Hill KM, Jonnalagadda SS, Albertson AM, et al. 2012. Top food sources contributing to vitamin D intake and the association of ready-to-eat cereal and breakfast consumption habits to vitamin D intake in Canadians and United States Americans. J Food Sci 77:H170–H175.
Holick MF. 2004. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80:1678S–1688S.
Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. 2011. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96:1911–1930.
Hollis BW, Johnson D, Hulsey TC, et al. 2011. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. J Bone Miner Res 26:2341–2357.
Hollis BW, Pittard WB III, Reinhardt TA. 1986. Relationships among vitamin D, 25-hydroxyvitamin D, and vitamin D-binding protein concentrations in the plasma and milk of human subjects. J Clin Endocrinol Metab 62:41–44.
Hollis BW, Wagner CL. 2011. Vitamin D requirements and supplementation during pregnancy. Curr Opin Endocrinol Diabetes Obes 18:371–375.
Hoogenboezem T, Degenhart HJ, de Muinck Keizer-Schrama SM, et al. 1989. Vitamin D metabolism in breast-fed infants and their mothers. Pediatr Res 25:623–628.
Hossain N, Khanani R, Hussain-Kanani F, et al. 2011. High prevalence of vitamin D deficiency in Pakistani mothers and their newborns. Int J Gynaecol Obstet 112:229–233.
Hossein-nezhad A, Holick MF. 2012. Optimize dietary intake of vitamin D: an epigenetic perspective. Curr Opin Clin Nutr Metab Care 15:567–579.
Hughes AM, Lucas RM, Ponsonby AL, et al. 2011. The role of latitude, ultraviolet radiation exposure and vitamin D in childhood asthma and hayfever: an Australian multicenter study. Pediatr Allergy Immunol 22:327–333.
Hypponen E. 2011. Preventing vitamin D deficiency in pregnancy: importance for the mother and child. Ann Nutr Metab 59:28–31.
Hypponen E, Berry DJ, Wjst M, et al. 2009. Serum 25-hydroxyvitamin D and IgE—a significant but nonlinear relationship. Allergy 64:613–620.
Hypponen E, Laara E, Reunanen A, et al. 2001. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358:1500–1503.
Institute of Medicine. 1997. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D and fluoride. Washington, D.C.: National Academies Press. p. 1–522.
Institute of Medicine. 2011. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary reference intakes for calcium and vitamin D. Washington, D.C.: The National Academies Press.
Johnson DD, Wagner CL, Hulsey TC, et al. 2011. Vitamin D deficiency and insufficiency is common during pregnancy. Am J Perinatol 28:7–12.
Kalra P, Das V, Agarwal A, et al. 2012. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. Br J Nutr 108:1052–1058.
Karohl C, Vaccarino V, Veledar E, et al. 2012. Vitamin D status and coronary flow reserve measured by positron emission tomography: a Co-Twin Control study. J Clin Endocrinol Metab 98:389–397.
Kehler L, Verma S, Krone R, Roper E. 2012. Vitamin D deficiency in children presenting to the emergency department: a growing concern. Vitamin D deficiency in Birmingham's children: presentation to the emergency department. Emerg Med J 0:1–3. doi:10.1136/emermed-2012-201473.
Koch MW, Metz LM, Agrawal SM, et al. 2013. Environmental factors and their regulation of immunity in multiple sclerosis. J Neurol Sci 324:10–16.
Kupferschmidt K. 2012. Uncertain verdict as vitamin D goes on trial. Science 337:1476–1478.
Larriba MJ, Ordonez-Moran P, Chicote I, et al. 2011. Vitamin D receptor deficiency enhances Wnt/beta-catenin signaling and tumor burden in colon cancer. PLoS One 6:e23524.
Lau SL, Gunton JE, Athayde NP, et al. 2011. Serum 25-hydroxyvitamin D

and glycated haemoglobin levels in women with gestational diabetes mellitus. Med J Aust 194:334–337.
Leffelaar ER, Vrijkotte TG, van Eijsden M. 2010. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. Br J Nutr 104:108–117.
Liu J. 2012. Vitamin D content of food and its contribution to vitamin D status: a brief overview and Australian focus. Photochem Photobiol Sci 11:1802–1807.
Liu N, Kaplan AT, Low J, et al. 2009. Vitamin D induces innate antibacterial responses in human trophoblasts via an intracrine pathway. Biol Reprod 80:398–406.
Liu NQ, Hewison M. 2011. Vitamin D, the placenta and pregnancy. Arch Biochem Biophys 523:37–47.
Liu NQ, Kaplan AT, Lagishetty V, et al. 2011. Vitamin D and the regulation of placental inflammation. J Immunol 186:5968–5974.
Liu PT, Stenger S, Li H, et al. 2006. Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. Science 311:1770–1773.
Louw JA, Werbeck A, Louw ME, et al. 1992. Blood vitamin concentrations during the acute-phase response. Crit Care Med 20:934–941.
MacLaughlin J, Holick MF. 1985. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 76:1536–1538.
Maiya S, Sullivan I, Allgrove J, et al. 2008. Hypocalcaemia and vitamin D deficiency: an important, but preventable, cause of life-threatening infant heart failure. Heart 94:581–584.
Malham M, Jorgensen SP, Ott P, et al. 2011. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. World J Gastroenterol 17:922–925.
Marya RK, Rathee S, Manrow M. 1987. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Invest 24:38–42.
McAree T, Jacobs B, Manickavasagar T, et al. 2013. Vitamin D deficiency in pregnancy—still a public health issue. Matern Child Nutr 9:23–30.
McCollum EV, Simmonds N, Becker JE. 1922. Nutrition classics from The Journal of Biological Chemistry 53:293–312, 1922. Studies of experimental rickets. XXI. An experimental demonstration of the existence of a vitamin which promotes calcium depositor. Nutr Rev (1975) 33:48–50.
McGrath J, Saari K, Hakko H, et al. 2004. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res 67:237–245.
McGrath JJ, Burne TH, Feron F, et al. 2010. Developmental vitamin D deficiency and risk of schizophrenia: a 10-year update. Schizophr Bull 36:1073–1078.
Mensink GB, Fletcher R, Gurinovic M, et al. 2013. Mapping low intake of micronutrients across Europe. Br J Nutr Jan 14:1–19.
Milne M, Baran DT. 1985. Inhibitory effect of maternal alcohol ingestion on rat pup hepatic 25-hydroxyvitamin D production. Pediatr Res 19:102–104.
Moore CE, Murphy MM, Holick MF. 2005. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr 135:2478–2485.
Mosekilde L. 2005. Vitamin D and the elderly. Clin Endocrinol (Oxf) 62:265–281.
Mostafa GA, Al-Ayadhi LY. 2012. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. J Neuroinflammation 9:201.
National Institutes of Health State-of-the-Science Panel. 2007. National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. Am J Clin Nutr 85:257S–264S.
Nesby-O'Dell S, Scanlon KS, Cogswell ME, et al. 2002. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: third National Health and Nutrition Examination Survey, 1988–1994. Am J Clin Nutr 76:187–192.
Novakovic B, Galati JC, Chen A, et al. 2012. Maternal vitamin D predominates over genetic factors in determining neonatal circulating vitamin D concentrations. Am J Clin Nutr 96:188–195.
Nowson CA, Margerison C. 2002. Vitamin D intake and vitamin D status of Australians. Med J Aust 177:149–152.
Nurmatov U, Devereux G, Sheikh A. 2011. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. J Allergy Clin Immunol 127: 724–733 e721–e730.
O'Loan J, Eyles DW, Kesby J, et al. 2007. Vitamin D deficiency during various stages of pregnancy in the rat; its impact on development and behaviour in adult offspring. Psychoneuroendocrinology 32:227–234.
Obican SG, Jahnke GD, Soldin OP, et al. 2012. Teratology Public Affairs Committee position paper: iodine deficiency in pregnancy. Birth Defects Res A Clin Mol Teratol 94:677–682.
Oken E, Ning Y, Rifas-Shiman SL, et al. 2007. Diet during pregnancy and risk of preeclampsia or gestational hypertension. Ann Epidemiol 17:663–668.
Ozkan S, Jindal S, Greenseid K, et al. 2010. Replete vitamin D stores predict reproductive success following in vitro fertilization. Fertil Steril 94:1314–1319.
Palm TA. 1888. Letter to the editor. Br Med J 2:1247.
Pandita KK, Razdan S, Kudyar RP, et al. 2012. "Excess gooD can be Dangerous". A case series of iatrogenic symptomatic hypercalcemia due to hypervitaminosis D. Clin Cases Miner Bone Metab 9:118–120.
Pani MA, Knapp M, Donner H, et al. 2000. Vitamin D receptor allele combinations influence genetic susceptibility to type 1 diabetes in Germans. Diabetes 49:504–507.
Patterson KY, Phillips KM, Horst RL, et al. 2010. Vitamin D content and variability in fluid milks from a US Department of Agriculture nationwide sampling to update values in the National Nutrient Database for Standard Reference. J Dairy Sci 93:5082–5090.
Paul G, Brehm JM, Alcorn JF, et al. 2012. Vitamin D and asthma. Am J Respir Crit Care Med 185:124–132.
Pawley N, Bishop NJ. 2004. Prenatal and infant predictors of bone health: the influence of vitamin D. Am J Clin Nutr 80:1748S–1751S.
Pereira F, Barbachano A, Singh PK, et al. 2012. Vitamin D has wide regulatory effects on histone demethylase genes. Cell Cycle 11:1081–1089.
Poel YH, Hummel P, Lips P, et al. 2012. Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med 23:465–469.
Powe CE, Seely EW, Rana S, et al. 2010. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hypertension 56:758–763.
Prentice A. 2008. Vitamin D deficiency: a global perspective. Nutr Rev 66: S153–S164.
Ralph AR, Lucas RM, Norval M. 2013. Vitamin D and solar ultraviolet radiation in the risk and treatment of tuberculosis. Lancet Infect Dis 13:77–88.
Ramagopalan SV, Dyment DA, Cader MZ, et al. 2011. Rare variants in the CYP27B1 gene are associated with multiple sclerosis. Ann Neurol 70:881–886.
Rawson JB, Sun Z, Dicks E, et al. 2012. Vitamin D intake is negatively associated with promoter methylation of the Wnt antagonist gene DKK1 in a large group of colorectal cancer patients. Nutr Cancer 64:919–928.
Reinholz M, Ruzicka T, Schauber J. 2011. Vitamin D and its role in allergic disease. Clin Exp Allergy 42:817–826.
Reis JP, von Muhlen D, Miller ER III, et al. 2009. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics 124:e371–e379.
Robinson CJ, Alanis MC, Wagner CL, et al. 2010. Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. Am J Obstet Gynecol 203:366 e361–366 e366.
Robinson CJ, Wagner CL, Hollis BW, et al. 2011. Maternal vitamin D and fetal growth in early-onset severe preeclampsia. Am J Obstet Gynecol 204:556 e551–556 e554.
Rosen CJ, Adams JS, Bikle DD, et al. 2012. The nonskeletal effects of vitamin D: an Endocrine Society scientific statement. Endocr Rev 33:456–492.

Roth DE. 2011. Vitamin D supplementation during pregnancy: safety considerations in the design and interpretation of clinical trials. J Perinatol 31:449–459.

Sabetta JR, DePetrillo P, Cipriani RJ, et al. 2010. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PLoS One 5:e11088.

Sahu M, Das V, Aggarwal A, et al. 2009. Vitamin D replacement in pregnant women in rural north India: a pilot study. Eur J Clin Nutr 63:1157–1159.

Saijo T, Ito M, Takeda E, et al. 1991. A unique mutation in the vitamin D receptor gene in three Japanese patients with vitamin D-dependent rickets type II: utility of single-strand conformation polymorphism analysis for heterozygous carrier detection. Am J Hum Genet 49:668–673.

Sanders KM, Nicholson GC, Ebeling PR. 2013. Is High Dose Vitamin D Harmful? Calcif Tissue Int 92:191–206.

Soliman AT, El-Dabbagh M, Adel A, et al. 2010. Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. J Trop Pediatr 56:19–26.

Sundar IK, Rahman I. 2011. Vitamin D and susceptibility of chronic lung diseases: role of epigenetics. Front Pharmacol 2:50.

Swamy GK, Garrett ME, Miranda ML, et al. 2011. Maternal vitamin D receptor genetic variation contributes to infant birthweight among black mothers. Am J Med Genet A 155:1264–1271.

Tare M, Emmett SJ, Coleman HA, et al. 2011. Vitamin D insufficiency is associated with impaired vascular endothelial and smooth muscle function and hypertension in young rats. J Physiol 589:4777–4786.

Thomas GN, o Hartaigh B, Bosch JA, et al. 2012. Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome: the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. Diabetes Care 35:1158–1164.

Thorne-Lyman A, Fawzi WW. 2012. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 26 (Suppl 1):75–90.

Tshibangu K, Oosterwijck K, Doumont-Meyvis M. 1975. Effects of massive doses of ergocalciferol plus cholesterol on pregnant rats and their offspring. J Nutr 105:741–758.

Tsiaras WG, Weinstock MA. 2011. Factors influencing vitamin D status. Acta Derm Venereol 91:115–124.

Urashima M, Segawa T, Okazaki M, et al. 2010. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr 91:1255–1260.

Uriu-Adams JY, Keen CL. 2010. Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development. Birth Defects Res B Dev Reprod Toxicol 89:313–325.

Urrutia RP, Thorp JM. 2012. Vitamin D in pregnancy: current concepts. Curr Opin Obstet Gynecol 24:57–64.

Uysal S, Kalayci AG, Baysal K. 1999. Cardiac functions in children with vitamin D deficiency rickets. Pediatr Cardiol 20:283–286.

Vandevijvere S, Amsalkhir S, Van Oyen H, et al. 2012. High prevalence of vitamin D deficiency in pregnant women: A National Cross-Sectional Survey. PLoS One 7:e43868.

Vidailhet M, Mallet E, Bocquet A, et al. 2012. Vitamin D: still a topical matter in children and adolescents. A position paper by the Committee on Nutrition of the French Society of Paediatrics. Arch Pediatr 19:316–328.

Vieth R. 1999. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 69:842–856.

Viljakainen HT, Korhonen T, Hytinantti T, et al. 2011. Maternal vitamin D status affects bone growth in early childhood—a prospective cohort study. Osteoporos Int 22:883–891.

Viljakainen HT, Saarnio E, Hytinantti T, et al. 2010. Maternal vitamin D status determines bone variables in the newborn. J Clin Endocrinol Metab 95:1749–1757.

Wagner CL, Hulsey TC, Fanning D, et al. 2006. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med 1:59–70.

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 pii: S0960-0760(13)00006-X. doi: 10.1016/j.jsbmb.2013.01.002.

Walker VP, Zhang X, Rastegar I, et al. 2011. Cord blood vitamin D status impacts innate immune responses. J Clin Endocrinol Metab 96:1835–1843.

Wang L, Ma J, Manson JE, Buring JE, Gaziano JM, Sesso HD. A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms, and risk of hypertension in men. Eur J Nutr 2012. doi: 10.1007/s00394-012-0480-8.

Wang L, Song Y, Manson JE, et al. 2012. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes 5:819–829.

Wang TJ, Zhang F, Richards JB, et al. 2010. Common genetic determinants of vitamin D insufficiency: a genome-wide association study. Lancet 376:180–188.

Wei SQ, Qi HP, Luo ZC, Fraser WD. 2013. Maternal vitamin D status and adverse pregnancy outcomes: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013 [Epub ahead of print].

Weisberg P, Scanlon KS, Li R, et al. 2004. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. Am J Clin Nutr 80:1697S–1705S.

Weisse K, Winkler S, Hirche F, et al. 2013. Maternal and newborn vitamin D status and its impact on food allergy development in the German LINA cohort study. Allergy 68:220–228.

Wijnia JW, Wielders JP, Lips P, et al. 2013. Is vitamin D deficiency a confounder in alcoholic skeletal muscle myopathy? Alcohol Clin Exp Res 37 (Suppl 1):E209–E215.

Willer CJ, Dyment DA, Sadovnick AD, et al. 2005. Timing of birth and risk of multiple sclerosis: population based study. BMJ 330:120.

Winzenberg TM, Powell S, Shaw KA, Jones G. 2010. Vitamin D supplementation for improving bone mineral density in children. Cochrane Database Syst Rev 2010;CD006944. doi: 10.1002/14651858.CD006944.pub2.

Wortsman J, Matsuoka LY, Chen TC, et al. 2000. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 72:690–693.

Yorifuji J, Yorifuji T, Tachibana K, et al. 2008. Craniotabes in normal newborns: the earliest sign of subclinical vitamin D deficiency. J Clin Endocrinol Metab 93:1784–1788.

Yoshizawa T, Handa Y, Uematsu Y, et al. 1997. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. Nat Genet 16:391–396.

Yu CK, Sykes L, Sethi M, et al. 2009. Vitamin D deficiency and supplementation during pregnancy. Clin Endocrinol (Oxf) 70:685–690.

Zhu H, Wang X, Shi H, Su S, Harshfield GA, Gutin B, Snieder H, Dong Y. A Genome-wide methylation study of severe vitamin D deficiency in African American adolescents. J Pediatr 2012. pii: S0022-3476(12)01272-3. doi: 10.1016/j.jpeds.2012.10.059.

Ziaei S, Norrozi M, Faghihzadeh S, et al. 2007. A randomised placebo-controlled trial to determine the effect of iron supplementation on pregnancy outcome in pregnant women with haemoglobin $>$ or $=$ 13.2 g/dl. BJOG 114:684–688.

Zosky GR, Berry LJ, Elliot JG, et al. 2011. Vitamin D deficiency causes deficits in lung function and alters lung structure. Am J Respir Crit Care Med 183:1336–1343.