

Future health implications of prenatal and early-life vitamin D status

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Current or recent low vitamin D status (or proxy measures such as dietary intake or ambient ultraviolet radiation) is linked to several chronic diseases, including osteoporosis, cancers, and cardiovascular and autoimmune diseases. Low prenatal vitamin D status may also increase susceptibility to such diseases in later life via specific target organ effects and/or through changes to the developing immune system. Maternal vitamin D supplementation during pregnancy could be an important public health measure to decrease risk of a range of chronic diseases, but further research is required to clarify beneficial and adverse effects of high prenatal vitamin D.

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INTRODUCTION

Recent research implicates vitamin D insufficiency as a risk factor for a variety of chronic diseases including multiple sclerosis, type 1 and type 2 diabetes, various cancers, osteoporosis, psychiatric illness, and cardiovascular diseases. Heightened susceptibility to at least some of these disorders may originate in early life,¹ with long-lasting structural or functional changes in developing organs or organ systems. Much of the existing literature on prenatal vitamin D status has focused on a specific disease. Here, we review the research literature on the possible etiological role of prenatal and early-life vitamin D status in relation to a range of chronic diseases.

The biologically active form of vitamin D is a steroid hormone. Its precursors are derived principally from UVB (wavelengths 290–315 nm) irradiation of the skin, with only a small contribution from diet (though the proportion varies by location) or supplements. UVB-induced chemical rearrangement of 7-dehydrocholesterol in epidermal and dermal cell plasma membranes induces formation of previtamin D₃, which undergoes thermal isomerization to form vitamin D₃. This passes into the

extracellular space, is adsorbed by vitamin D binding protein in the dermal capillary bed, and drawn into the circulation. While oily fish also supply vitamin D₃, plant sources used in some vitamin D supplements provide vitamin D₂.

Following UV-induced synthesis or ingestion, vitamin D (D₂ or D₃) is metabolized in the liver (involving the mitochondrial enzyme 25-hydroxylase)² to form 25(OH) vitamin D [25(OH)D], the main circulating form of vitamin D and the usual serum measure of vitamin D status. In the kidney (and, we now know, a range of target tissues), the 25(OH)D 1 α -hydroxylase enzyme (1 α -hydroxylase) induces further hydroxylation, converting 25(OH)D to the biologically active hormone form 1,25(OH)₂D (or calcitriol). Catabolism of 25(OH)D or 1,25(OH)₂D to less active metabolites (by vitamin D 24 hydroxylase) provides regulatory feedback control of vitamin D-induced gene transcription.³ Circulating 1,25(OH)₂D enters cells by passive diffusion and binds to a nuclear vitamin D receptor (VDR), causing a conformational change that allows the VDR to dimerize with the retinoid X receptor.⁴ The subsequent interaction with the vitamin D response element (VDRE) on target genes initiates gene transcription.

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Table 1 Variation in recommended vitamin D intake for (non-high-risk) pregnant women and infants.

Country [Reference]	Pregnant and breastfeeding women	Infants <12 mo.
USA [Gartner and Greer (2003) ¹⁶]	200 IU/day	200 IU
Canada [Canadian Pediatric Society (2007) ¹⁷]	Consider 2000 IU/day (esp. in winter)	400 IU/day (breastfed) 800 IU/day (winter >55°N)
Canada [Health Canada (2004) ¹⁸]	200 IU/day	400 IU/day (breastfed)
United Kingdom [UK Dept of Health (2008) ¹⁹]	400 IU/day	340 IU/day (decreasing to 200 IU/day after 6 months)
Australia and New Zealand [NHMRC (2005) ²⁰]	200 IU/day	200 IU/day

VDRs and/or 1α -hydroxylase have been identified in a wide range of cells, including the following: small intestine, osteoblasts, activated T and B lymphocytes, β -islet cells, most organs (brain, heart, skin, gonads, prostate, breast), and mononuclear cells.^{5,6} The active $1,25(\text{OH})_2\text{D}$ increases intestinal calcium absorption,⁷ facilitates mineralization of the skeleton,⁸ promotes cellular differentiation and apoptosis, stimulates insulin production,⁹ promotes TSH secretion,¹⁰ improves myocardial contractility,¹¹ and possibly inhibits tumor invasion and angiogenesis.¹² Within the immune system, $1,25(\text{OH})_2\text{D}$ inhibits Th-1 type immune function in adult (memory) cells, induces T regulatory cells, and enhances phagocytosis by white blood cells.¹³ In cord blood (naïve) T cells, $1,25(\text{OH})_2\text{D}$ appears to inhibit both Th-1 and Th-2 differentiation,¹⁴ but the role of vitamin D in fetal and early postnatal life is not well understood.

MATERNAL AND FETAL VITAMIN D

During pregnancy, increased maternal intestinal calcium absorption, facilitated by increased levels of $1,25(\text{OH})_2\text{D}$, ensures the availability of extra calcium required for fetal skeletal growth.¹⁵ Recommended vitamin D intakes vary up to 10-fold (Table 1). Maternal serum $25(\text{OH})\text{D}$ concentrations may decrease, particularly in the third trimester, but serum $1,25(\text{OH})_2\text{D}$ concentrations increase 50 to 100% over the non-pregnant state during the second trimester and by 100% during the third trimester.²¹

Concentrations of $25(\text{OH})\text{D}$ and $1,25(\text{OH})_2\text{D}$ are generally low in fetal, compared to maternal, blood.^{22,23} At birth, umbilical cord $25(\text{OH})\text{D}$ levels are directly correlated with maternal levels.^{22,24} There is inconsistent evidence of transplacental transfer of $1,25(\text{OH})_2\text{D}$ from mother to fetus at physiological levels,^{22,25} although this may be significant at pharmacological doses.²⁶ The placenta itself contains 1α -hydroxylase²⁷ and fetal $1,25(\text{OH})_2\text{D}$ may be synthesized there, as required for calcium homeostasis,²⁶ with a major contribution from the fetal kidney^{26,28} (Figure 1).

Issues relevant to maternal vitamin D: diet, skin color, sun avoidance, location, and season

Vitamin D requirements during pregnancy must be met through dietary intake (consumption of fish or supplemented foodstuffs), supplements, and sun exposure. The efficiency and amount of ultraviolet B radiation (UVB)-induced production of vitamin D depends on the dose of relevant wavelengths of ultraviolet radiation (UVR) to skin precursors. That dose, in turn, depends on ambient UVB (variable by season, time of day, and location), skin pigmentation (with darker skin reducing the effective UVB dose to epidermal cells) and barriers (sun protection measures and clothing).^{29,30} Women who are pregnant at high-latitude locations or during winter are at increased risk of vitamin D insufficiency. Furthermore, those who are effectively sun-protected, e.g. dark-skinned and/or veiled women,³¹ are at increased risk even in high ambient UVR environments.³²

Observations of seasonal or latitudinal patterns of disease occurrence often provide the first indication of a possible prenatal or early postnatal vitamin D effect: increased incidence with winter or spring season of birth, birth at higher latitudes, or birth in urban environments (compared to rural). Such evidence is non-specific,

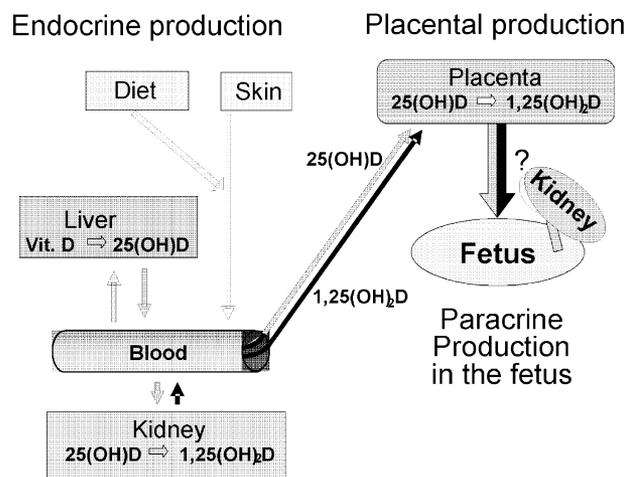


Figure 1 Feto-maternal vitamin D production.

requiring support from animal and human studies before any causality can be inferred. In the following outcome-specific sections, evidence-to-date (summarized in Table 2) is reviewed following this progression of evidence, where such evidence is available. Although there is now considerable research linking VDR polymorphisms to a variety of health outcomes (e.g., bone mineral density,⁴² multiple sclerosis,⁸⁵ type 1 diabetes,⁸⁶ and asthma⁸⁷), this work is not considered since the functional significance of these polymorphisms is not yet clear and it has not been established that they can be used as an instrumental variable for prenatal vitamin D status.

Vitamin D and obstetric outcomes

Ovarian function (vitamin D-modulated) and spermatogenesis (calcium-dependent) may be impaired in vitamin D-deficient rats, resulting in reduced fertility and litter size.²⁷ Furthermore, murine gene knockout models for 1α -hydroxylase and VDR are infertile.³ Some,⁸⁸ but not all,⁷⁸ experimental work shows reduced fetal growth in rats whose mothers were vitamin D deficient.

There is increased expression of 1α -hydroxylase and VDR genes³ and high levels of 1α -hydroxylase²⁷ in human placental and decidual tissue during the first and early second trimesters. Maintenance of adequate local $1,25(\text{OH})_2\text{D}$ levels may be required for induction of immune tolerance of implantation and successful maintenance of pregnancy, via dampening of Th1 immune function.^{3,27}

One study showed lower maternal $1,25(\text{OH})_2\text{D}$ serum levels in pre-eclamptic compared to normal pregnancies (43 versus 50 pg/mL).⁸⁹ Furthermore, pre-eclamptic placentas may have decreased ability to convert $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$,⁹⁰ despite increased 1α hydroxylase and decreased 25 -hydroxylase and 24 -hydroxylase gene expression, compared to normal placental tissue.⁹¹ Intriguingly, in the Northern Finland Birth Cohort, the risk of pre-eclampsia was halved (OR = 0.49, 95% CI 0.26–0.92) in first pregnancies of women who received vitamin D supplementation during their own first year of life.³⁷

Studies indicate that babies born to mothers with low $25(\text{OH})\text{D}$ levels or vitamin D intake may have the following:

- shorter gestation (by 0.7 week; 95% CI -1.3 – -0.1 in one study only);³³
- lower birth weight, with each additional 40 IU of vitamin D intake (diet + supplements) associated with an 11 g (95%CI 1.2–20.7) increase in birth weight, although the findings have not been consistent, with some studies showing little or no effect;^{35,36}
- shorter knee-heel length (a marker of intrauterine long bone growth) (4.3 mm smaller, 95% CI -7.3 – -1.3).³³

In a double-blind trial of vitamin D supplementation of women during the last trimester of pregnancy in the United Kingdom, there was no significant difference in birth weight, body length, or head circumference between the babies of treated and control mothers. However, at 12 months of age, the supplemented group was significantly heavier (mean weight, 9.39 versus 8.98 kg) and longer (mean length, 76.2 versus 74.6 cm) than the control group, despite a lack of postnatal supplementation.³⁴

Vitamin D effects on bone health

Vitamin D insufficiency and deficiency (Table 3) result in inadequate mineralization of bone, causing rickets (children) and osteomalacia (adults).^{92,93} Fetal bone growth occurs mainly during the last trimester and relies on increased placental calcium transport capacity, which is partly controlled by vitamin D levels.⁴² Evidence is now emerging that maternal vitamin D status may influence bone health in offspring.⁹⁵

Studies demonstrating seasonality in child⁹⁶ or adult⁹⁷ stature related to month of birth and the finding of lower bone mineral content (BMC) in newborns born in winter compared to those born in summer⁴² are consistent (among other possible explanations) with a vitamin D effect on later bone health. Indeed, low vitamin D status, measured as serum $25(\text{OH})\text{D}$, during late pregnancy was associated with lower total and lumbar spine BMC in offspring at 9 years of age.^{42,44}

There are conflicting findings concerning the effects of early infantile vitamin D supplementation on later childhood bone health. In a small randomized trial administering vitamin D (either 500 IU/day or 1000 IU/day) with or without calcium and phosphorus supplementation, i.e., four groups, to 70 preterm infants, BMC at 3 months of age in a subgroup ($n = 37$) was higher in the 500 IU/day group than in the 1000 IU/day group.⁹⁸ Notably, $25(\text{OH})\text{D}$ levels were not significantly different between the two groups. At 9 years of age, there were no between-group differences in lumbar or radial BMC or BMD in the four groups (total $n = 35$). Meanwhile, in prepubertal girls (median age = 8 years) supplemented during the first year of life with 400 IU/day of vitamin D (as recalled by families and pediatricians), BMC and BMD at the femoral neck and femoral trochanter were significantly higher than in non-supplemented participants.⁹⁹ BMD but not BMC was significantly higher at the radial metaphysis.

Vitamin D status: a risk factor for central nervous system disorders?

There is considerable evidence from rodent studies that vitamin D is involved in normal brain development.¹⁰⁰

Table 2 Summary of relevant studies by the level of evidence for a role for lower prenatal or perinatal vitamin D in the causation of later health outcome.

Health outcome	Animal experimental studies	Human descriptive studies	Human observational analytic studies	Human experimental (intervention) studies
Shorter gestation			(+)Morley et al. (2006) ³³	
Shorter birth length			(+)Morley et al. (2006) ³³	
Low birth weight			(null)Morley et al. (2006), ³³ Brooke et al. (1981), ³⁴ Gale et al. (2008) ³⁵	(null) Brooke et al. (1981) ³⁴
Poorer postnatal growth			(+)Mannion et al. (2006) ³⁶	(+)Brooke et al. (1981) ³⁴
Pre-eclampsia			(+)Hypponen et al. (2007) ³⁷	
Asthma and/or atopy	(-)Matheu et al. (2003) ³⁸		(+)Camargo et al. (2007), ³⁹ Devereux et al. (2007) ⁴⁰	
			(-)Gale et al. (2008), ³⁵ Hypponen et al. (2004) ⁴¹	
Osteoporosis		(+)Cooper et al. (2005) ⁴²	(+)Dennison et al. (2001), ⁴³ Javaid et al. (2006) ⁴⁴	
Schizophrenia	(+)Almeras et al. (2007), ⁴⁵ Becker et al. (2005), ⁴⁶ Eyles et al. (2007), ⁴⁷ Eyles et al. (2006), ⁴⁸ O'Loan et al. (2007) ⁴⁹	(+)McGrath et al. (1995), ⁵⁰ McGrath et al. (1999), ⁵¹ McGrath et al. (2002), ⁵² McGrath et al. (2004), ⁵³ Morgan et al. (2001), ⁵⁴ Torrey et al. (1997) ⁵⁵ (null)Kendell (2002) ⁵⁶	(+)McGrath et al. (2004) ⁵³	
Cardiovascular diseases	(+)Morris et al. (1995) ⁵⁸ (-)Norman et al. (2002), ⁵⁹ Toda et al. (1985a), ⁶⁰ Toda et al. (1985b) ⁶¹	(null)Gale et al. (2008) ³⁵		
Brain tumors		(+)Brenner et al. (2004), ⁶² Ko et al. (2005) ⁶³		
Type 1 diabetes	(null)Hawa et al. (2004) ⁶⁴	(+)Songini et al. (2001), ⁶⁵ Ursic-Bratina et al. (2001), ⁶⁶ Willis et al. (2002), ⁶⁷ Staples et al. (2003) ⁶⁸ (null)Kida et al. (2000) ⁶⁹	(+)Eurodiab (1994), ⁷⁰ Fronczak et al. (2003), ⁷¹ Hypponen et al. (2001), ⁷² Stene et al. (2000), ⁷³ Zipitis et al. (2008) ⁷⁴	
Multiple sclerosis	(+)Almeras et al. (2007) ⁴⁵	(+)Staples et al. (2003), ⁶⁸ McLeod et al. (1994), ⁷⁵ Willer et al. (2005) ⁷⁶		
Other autoimmune diseases		(+)Van Ranst et al. (2005) ⁷⁷		
Nephrogenesis	(+)Maka et al. (2008) ⁷⁸			
Vitamin D deficiency during pregnancy		Many studies, e.g., Schroth et al. (2005), ⁷⁹ Nozza et al. (2001), ⁸⁰ Ramavat et al. (1999), ⁸¹ Pillow et al. (1995), ⁸² Nesby-O'Dell et al. (2002), ⁸³ Maghbooli et al. (2007), ²⁴ Lee et al. (2007) ⁸⁴		

Abbreviations: +, positive association, i.e., low levels increase risk and high levels decrease risk; -, negative association, i.e., low levels decrease risk and high levels increase risk; null, no evidence of an association.

Table 3 Clinical vitamin D status terminology, based on serum levels of 25(OH)D measured in nmol/L.

Vitamin D status	Current definition (variable)*	Proposed definition#
Sufficiency	>50	≥75
Insufficiency/mild deficiency	25–50	50–74.9
Deficiency	<25	<50

* Data from Munns et al. (2006).⁹²

Data from Alemzadeh (2008).⁹⁴

Genes encoding 25-hydroxylase, 1 α -hydroxylase, and 24-hydroxylase are expressed in brain cells,⁴⁵ while the VDR is present in the neuroepithelium during early neurogenesis and, at later stages, in the subventricular zone. The distributions of the VDR and 1 α -hydroxylase appear to be very similar in the brains of adult rats and humans.¹⁰¹

Brain size and function. At birth, rats with prenatal vitamin D deficiency had heavier and longer brains (which normalized by adulthood with postnatal restoration of vitamin D levels), enlarged lateral ventricles (with persistence into adulthood), and decreased cortical thickness.^{53,102,103} Additionally, there may be a critical window during late gestation in which vitamin D insufficiency precipitates an altered adult behavioral phenotype.⁴⁹

Evidence from human studies is scanty. One recent study found that higher maternal serum 25(OH)D in late pregnancy (<30 versus >75 nmol/L) was associated with larger head circumference of offspring at 9 years (52.6 versus 53.6 cm, *P* for trend 0.012),³⁵ but not with measures of cognition or psychological health.³⁵

Schizophrenia. Schizophrenia appears to be more common in relation to the following:

- urban versus rural birth;¹⁰⁴
- winter or spring birth (a 5–8% excess was described in the northern hemisphere⁵⁵ but was not confirmed in a meta-analysis of southern hemisphere studies);⁵¹
- dark-skinned migrants to northwestern Europe (compared to the white population);¹⁰⁵
- low duration of sunshine in the months immediately before and after birth, for males only.⁵²

In rats, offspring of vitamin D-deficient mothers had significant impairment of latent inhibition (ability to ignore irrelevant stimuli), a feature often associated with schizophrenia, while those transiently depleted showed subtle and discrete alterations in learning and memory.⁴⁶

In the Finnish birth cohort study, there was reduced risk of schizophrenia in males (but not females) with regular (RR = 0.08, 95% CI 0.01–0.95) or irregular (RR = 0.12, 95% CI 0.02–0.90) vitamin D supplementation (maternal self-report) during the first year of life.⁵⁷

Autism. There is scanty evidence for an association of low maternal vitamin D with risk of autism. Season-of-birth findings are inconsistent, with some showing an increased risk with March (early spring) birth but others finding no effect or implicating other months.¹⁰⁶ Children of dark-skinned mothers, particularly immigrants to low ambient UVR locations, may be at increased risk, but this finding has been inconsistent.¹⁰⁷

Brain tumors and epilepsy. Ko et al.⁶³ noted an excess of winter births in children with astrocytomas and ependymomas, and suggested this may reflect increased cellular proliferation found in the developing brains of embryos exposed to low prenatal vitamin D or by alteration of epigenetic programs established during early brain development. A similar pattern of excess winter birth has been demonstrated in adult glioma patients (peak in winter, trough in summer), which is consistent with seasonal variation in exposure to an intrauterine or environmental factor during the pre- or early postnatal period.⁶² Interestingly, an excess of winter births (December–March) has also been noted in adults with epilepsy.¹⁰⁸

Multiple sclerosis (MS). Latitudinal gradients in MS prevalence and incidence are well known.^{75,109} In a very large cohort of MS cases from the northern hemisphere, Willer et al.⁷⁶ reported a striking season-of-birth pattern in patients with MS (Figure 2).

Direct prospective data on prenatal or early postnatal vitamin D status and subsequent MS risk are not available. However, past childhood sun exposure¹¹⁰ or higher serum 25(OH)D in early adulthood¹¹¹ have been associated with reduced MS risk.

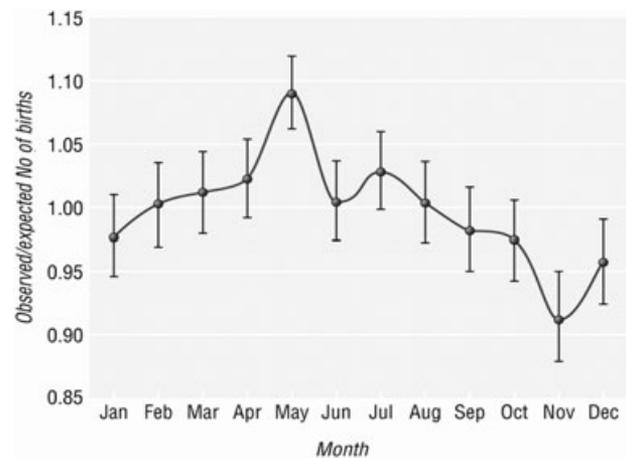


Figure 2 Pooled analysis of observed/expected births in people with multiple sclerosis in Canadian, British, Danish, and Swedish studies (*n* = 42,045) with 95% confidence intervals.

Reproduced from Willer et al. (2005)⁷⁶ with permission from the BMJ Publishing Group.

One hypothesis, consistent with the ecological and observational data and a described maternal parent-of-origin effect,^{112,113} is that low wintertime vitamin D levels at some critical point of brain or immune system development, either during gestation or shortly after birth, increases risk of later development of MS.⁷⁶

Vitamin D and other autoimmune disorders

Type 1 diabetes (T1D). T1D prevalence⁶⁸ and incidence^{114,115} increase with increasing (absolute) latitude in homogeneous populations. Although there are conflicting findings, several studies show increased risk of T1D with summer birth and decreased risk with winter birth, compared to population controls.^{67,116,117} This would be consistent with, among many other possible explanations, an effect of low vitamin D status acting at around 3–4 months gestational age, i.e., during the preceding winter.

Experimental studies in the non-obese diabetic mouse model of type 1 diabetes show no protective effect of vitamin D intake either prenatally or in infancy.⁶⁴ However, in human studies there was a 63% decreased risk of islet cell antibodies (adjusted OR = 0.37, 95% CI 0.17–0.78) in offspring with a single standard deviation (156 IU) increase in recalled maternal dietary vitamin D intake during pregnancy.⁷¹ Similarly, higher maternal cod liver oil (a potent source of vitamin D) intake during pregnancy was associated with decreased risk of T1D in offspring (adjusted OR = 0.36, 95% CI 0.14–0.90).⁷³

There is consistent evidence from observational analytic human studies of a decreased risk of T1D with early childhood vitamin D supplementation, as in the following:

- Multicenter case control study, early childhood supplementation: adjusted OR = 0.67, 95% CI 0.53–0.86;⁷⁰
- Prospective cohort study, vitamin D supplementation in the first year of life (versus no supplementation): adjusted RR = 0.12, 95% CI 0.03–0.51;⁷²
- Meta-analysis of case-control studies, infant vitamin D supplementation: pooled OR = 0.71, 95% CI 0.60–0.84, with some evidence of a dose-response effect.⁷⁴

Crohn's disease. Summer season of birth was associated with lower risk of later development of Crohn's disease (OR = 0.64, 95% CI 0.44–0.91) in one study.⁷⁷ However, the role of early-life vitamin D intake or status in the onset of Crohn's disease, a Th-1-mediated autoimmune disease, has not been studied to date.

Vitamin D and asthma

Both adverse and beneficial effects on asthma risk have been described for higher prenatal and early postnatal vitamin D intake.

Vitamin D as a possible protective factor for asthma. Lower maternal vitamin D intake during pregnancy was found to be associated with decreased bronchodilator responsiveness and increased wheezing symptoms in children at age 5 years: adjusted OR (for 100 IU increase in maternal vitamin D intake) = 0.81, 95% CI 0.74–0.89. The latter protective effect of vitamin D intake was strongest when the last menstrual period was in winter (adjusted OR = 0.62, 95% CI 0.47–0.83) compared with other seasons (adjusted OR = 0.85, 95% CI 0.75–0.97).^{39,40}

In Central Europe, babies of Caucasian mothers born in the winter months (mid-October to mid-April) had lower mean 25(OH)D levels in cord blood (26.2 nmol/L, 95% CI 18.3–42.5 nmol/L) and higher IgE levels (0.62 IU/mL, 95% CI 0.18–2.60 IU/mL) than those born in the summer months (52.2 nmol/L, 95% CI 29.5–65.3 nmol/L and 0.36 IU/mL, 95% CI 0.09–1.00 IU/mL), respectively.¹¹⁸ There was a direct correlation between 25(OH)D levels and IL-10 levels ($r = 0.22$), and a lower IL-10 to IgE ratio in the winter-born, low 25(OH)D group (2.24, 95% CI 0.43–10.20 versus 5.02, 95% CI 1.6–42.7 pg/IU). In view of the role of IL-10 in the development of tolerance to exogenous antigens and inhibiting mast cell degranulation,¹¹⁸ these findings are consistent with low vitamin D status at birth increasing the risk of an allergic propensity.

Vitamin D as an adverse risk factor for asthma. There is a parallel temporal relationship between rising prevalence of allergic diseases and increasing use of infant vitamin D supplementation.¹¹⁹ Furthermore, asthma prevalence appears to increase with decreasing latitude (higher ambient UVR and therefore an expectation of higher vitamin D status).^{68,120,121} However, confounding by other factors, e.g., latitude-related allergen levels, has not been evaluated.

In the Finnish Birth Cohort, regular vitamin D supplementation in the first year of life (>2000 IU/day versus irregular or no supplementation) was associated with an increased risk of asthma (adjusted OR = 1.33, 95% CI 0.97–1.82), atopy (at least one positive skin prick test; adjusted OR = 1.33, 95% CI 1.07–1.64) and allergic rhinitis (adjusted OR = 1.33, 95% CI 1.12–1.58) at age 31 years.⁴¹ Similarly, in the UK, higher maternal serum 25(OH)D levels during late pregnancy (>75 versus <30 nmol/L) were associated with an increased risk of eczema at 9 months (OR = 3.26, 95% CI 1.15–9.29) and asthma at age 9 years (OR = 5.40, 95% CI 1.09–26.65).³⁵

These apparently conflicting findings may suggest that timing of exposure to lower or higher vitamin D levels is also important – with a protective effect early in gestation but an increased risk postnatally. Further work is required to account for the timing of variation in vitamin D status.

Vitamin D effects on cardiovascular disease and metabolic syndrome risk

There is considerable evidence linking vitamin D insufficiency in adulthood with hypertension, impaired β cell function, the metabolic syndrome, obesity, and heart disease.^{9,94,122–125}

In neonatal rats exposed prenatally to low maternal serum 25(OH)D levels, there was a general slowing of cardiac development, with significantly lower heart weights (143 versus 174 g), decreased citrate synthase and 3-hydroxyacyl CoA dehydrogenase activity and a 15% lower myofibrillar protein content.⁵⁸

However, administration of very high-dose vitamin D to rats (considerably higher than would be administered to humans) during gestation and early development resulted in adverse changes in elastin content and organization in the aorta consistent with increased later risk of hypertension or aneurysm.⁵⁹ Nevertheless, two studies in pigs, where vitamin D doses achieved serum 25(OH)D levels approximating recommended human levels and showed adverse effects on vasculature: prenatal administration to two sows was associated with coronary lesions in offspring at 6 weeks,⁶⁰ early postnatal administration ($n = 187$) was associated with intimal thickening and degenerate smooth muscle cells typical of vascular ageing.⁶¹

In the 1960s, abnormal large vessel calcification and supravalvular aortic stenosis in association with severe infantile hypercalcemia was hypothesized to be linked to concurrent use of multiple foodstuffs containing vitamin D in the UK and elsewhere.¹²⁶ Despite supportive animal evidence,¹²⁷ it is now recognized that these features are typical of William's Syndrome, caused by a genetic mutation that also involves abnormal vitamin D metabolism.¹²⁸ Indeed, a recent longitudinal study found no statistically significant associations between maternal 25(OH)D levels and cardiac measures in offspring at 9 years, including in blood pressure, carotid intima-media thickness, arterial compliance, and cardiac structure.³⁵

Effect of vitamin D on other organs

There is mounting evidence in adults that higher vitamin D levels decrease risk of prostate cancer onset or mortality.¹²⁹ In rats, offspring of mothers injected with vitamin D during pregnancy had greater mean prostatic weight (pre-pubertal, 35% increase; adulthood, 68% increase) compared to offspring of mothers receiving vehicle only and a histologically more differentiated and mature prostatic architecture.¹³⁰ While it is possible that such changes, determined prenatally, might be protective for the later development of prostate cancer, considerable further research is required.

Maternal vitamin D deficiency in rats stimulated nephrogenesis in offspring, with a 20% increase in nephron number, but a decrease in renal corpuscle size, observed between replete and deficient rats, despite there being no difference in body weight, or kidney weight and volume.⁷⁸ Whether this finding is replicable in humans or is of functional significance has yet to be determined.

Intriguingly, a recent study showed that in women aged 18–79 years, leukocyte telomere length was positively and significantly correlated with serum vitamin D concentration ($r = 0.07$).¹³¹ This relationship persisted after adjustments were made for multiple covariates. The difference in telomere length between the highest and lowest tertiles of serum 25(OH)D concentration was equivalent to 5.0 years of telomeric aging. Whether or not this finding is replicable and the possible implications in relation to future health effects of fetal vitamin D status require further research.

IMPLICATIONS FOR CURRENT POLICY

Maternal vitamin D supplementation could potentially be an important public health measure to decrease risk for a range of chronic diseases. However, the optimal levels for pregnant mothers and their infants are not known. Internationally, there is considerable variation in the recommended vitamin D intake for pregnant women and infants. A tenfold difference in recommended intake is found between Canada and some other countries (Table 1). This is not merely a theoretical issue but one of large and immediate importance, as evidenced by the current recommendations, which represent a form of population intervention.

CONCLUSION

This review of the possible health consequences of maternal and neonatal vitamin D status and intake indicates that vitamin D supplementation may have profound effects not only for bone health but possible beneficial effects for Th-1 autoimmune diseases, schizophrenia, brain tumors, and asthma. However, the possible adverse effects of vitamin D on cardiovascular health and allergy should also be considered. Critical windows of exposure to adequate vitamin D levels during fetal maturation remain to be defined. Further work should also include examination of large birth cohorts where there are good measures of fetal or maternal vitamin D intake or vitamin D status and long-term health outcomes to better understand the net risks and benefits of a given maternal and early postnatal vitamin D status in relation to not only bone health, but a range of chronic diseases.

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