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Canadian Council of Food and Nutrition
Conseil canadien des aliments et de la nutrition

VITAMIN D: The Current State in Canada

A CCFN WATCHING BRIEF AUGUST 2008

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Vitamin D is considered an essential nutrient, with the main function widely accepted as being vital to maintain calcium homeostasis and bone health. Emerging roles for vitamin D point to prevention of not only osteoporosis, but also other chronic diseases including cancer, multiple sclerosis, diabetes and schizophrenia.

The volume of research related to vitamin D has increased vastly since the publication of the Dietary Reference Intakes (DRI) in 1997. Although vitamin D is produced endogenously through exposure to solar radiation, health care professionals agree upon diet as the safest source. The amount of dietary vitamin D now thought to be required for optimal status is much greater than that required to prevent a deficiency. In the coming months Health Canada will be working with the Institute of Medicine to refine the DRI framework and begin the revision of the DRIs on vitamin D and calcium. In the meantime, a number of societies have put forth higher targets for vitamin D intake and status with the goal to optimize health outcomes. The safety and effectiveness of these recommendations has yet to be proven.

Unfortunately, reports of vitamin D status in Canadians of all ages are not yet forthcoming. However, the state of vitamin D nutrition in Canada suggests that although vitamin D intakes are close to the Adequate Intake (AI) across all ages, vitamin D deficiency is common among all groups studied. Deficiency is present across the Canadian multicultural population from south to north and is likely a function of both limited endogenous synthesis and limited dietary sources.

The implication of these observations is that Canada's current health policy, food fortification policy and food supply will likely require updating if we are to achieve optimization of vitamin D status.

This Working Brief provides a summary of vitamin D nutrition across the lifespan in Canada and identifies gaps in knowledge that need to be addressed to improve vitamin D nutrition and food supply in Canada.

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[i] CCFN wishes to acknowledge Sheryl Conrad, B.Sc., RD, for her assistance in preparing this Watching Brief based on a more extensive report written by Dr. Hope Weiler, and editing the full report. The full report is available to CCFN members.

Dietary recommendations

The underpinning philosophy of dietary recommendations is to safely meet the needs of the majority of people. In 1997, the Institute of Medicine (IOM) published Dietary Reference Intake (DRI) values for vitamin D[1] to be used by both USA and Canada (Table 1).

Table 1: Dietary Reference Intakes for Vitamin D[1]

Life Stage Group (y)	**Adequate Intake** (IU/d)	**Tolerable Upper Intake Level** (IU/d)	**No Observed Adverse Effect Level** (IU/d)
Males and Females			
0 to 1	200	1000	2000
1 to 50	200	2000	2400
51 to 70	400	2000	2400
>70	600	2000	2400
Pregnancy and Lactation			
≤18 to 50	200	2000	2400

Note: This table combines some of the DRI age–sex groups where values are the same. DRI reports and tables are available on the Health Canada website: www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php.

The IOM acknowledged that exposure to sunlight may not be the best approach to ensuring adequate vitamin D status of populations as this can be dependent on culture, skin pigmentation, and/or behaviour related to use of sun block.[1,2] Thus, the Adequate Intake (AI) is designed to cover the needs of most individuals for vitamin D in the absence of exposure to ultraviolet beta solar radiation (UVB). The Tolerable Upper Intake Level (UL) for vitamin D was set to have the highest likelihood of safety for the public, based on the No Observed Adverse Effect Level.[1]

Background on DRI recommendations[1]

Age group	**Background on DRI recommendations**
Infants	It is assumed that physiological requirements for vitamin D are the same whether the infant is fed breast milk or formula, and that consuming one litre of formula or cows milk daily upon weaning provides 400 IU vitamin D. The IOM stated that 400 IU would not be excessive.
Children 1–8 years	There were no data upon which to base the AI; therefore, the AI value for this age group was extrapolated from data on older children.
Children 9–18 years	The IOM stated, "children who live in the far northern and southern latitudes may be unable to synthesize enough vitamin D in their skin to store for use in the winter. These children may need a vitamin D supplement."
Young adult and adult age groups	The IOM acknowledged that there was "little scientific information that related vitamin D intake, bone health and vitamin D status…in young adults and adult age groups".
Pregnant or lactating women	There was no reason to believe that pregnant or lactating women had increased needs for vitamin D.
Adults 51–70 years	The ability to synthesize vitamin D was acknowledged to decrease with age.
Adults >70 years	The IOM reported that "the evidence is strong that the elderly are at high risk for vitamin D deficiency, which causes secondary hyperparathyroidism and osteomalacia and exacerbates osteoporosis, resulting in increased risk of skeletal fractures."

Recommendations for vitamin D intake in all age groups are increasingly being scrutinized as more and more scientists, societies and institutions debate the adequacy based on a high prevalence of vitamin D deficiency in North America and throughout the world.

Health Canada promotes supplements for exclusively breastfed infants and for adults 50 years of age or older (Table 2). Higher recommendations for vitamin D intake are being promoted by disease-specific agencies (Table 2). In September 2007, the IOM held a 2-day conference on vitamin D[ii] to review the evidence-based science of vitamin D nutrition and bone health[3] and to begin looking forward to resolution of the discrepancy in recommendations and optimization of vitamin D status. At that meeting, the systematic review on vitamin D funded by the U.S. National Institutes of Health (NIH) was summarized.[3] Health Canada is continuing its collaboration with the IOM on the next generation of harmonized DRIs. Health Canada intends to contract with the Food and Nutrition Board of the IOM later in 2008 to develop a framework for the future revision of DRIs and a statement of work for the review of DRIs for vitamin D and calcium. In addition, Health Canada is updating guidelines for nutrition in pregnancy.[iii]

Table 2: Other Canadian Recommendations

Organization	Population Group	Recommended Vitamin D Intake
Health Canada (3)[iv]	Exclusively breastfed infants	400 IU/d supplement until 400 IU/d can be achieved through foods
Canada's Food Guide[4,v]	Adults >50 y	400 IU/d supplement
Canadian Pediatric Society working group[5,vi]	Infants in northern Native communities	800 IU/d during winter months
	Pregnant and lactating women	2000 IU/d supplement
Canadian Osteoporosis Society[6,vii]	Canadians 19–50 years, including pregnant or lactating women	400 IU/d vitamin D_3
	Adults >50 y	800 IU/d vitamin D_3
Canadian Cancer Society[viii]	Adults	consider 1000 IU/d supplement during fall and winter
	Adults at higher risk of having lower vitamin D levels (e.g. people who are older, who have dark skin, who do not go outside often, and/or who wear clothing that covers most of their skin)	consider 1000 IU/d supplement all year round
Canadian Dermatology Association[ix]	People who are concerned about vitamin D levels	1000 IU/d supplement
International panel that included Canadian experts[7]	Adults	1000 IU/d

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ii http://vitamindandhealth.od.nih.gov:80/default.aspx

iii The revised guidelines are expected in Summer 2008. See www.hc-sc.gc.ca/fn-an/nutrition/prenatal/index-eng.php for updates.

iv www.hc-sc.gc.ca/fn-an/nutrition/child-enfant/infant-nourisson/vita_d_supp-eng.php

v www.hc-sc.gc.ca/fn-an/food-guide-aliment/index-eng.php/index-eng.php

vi www.cps.ca/english/statements/II/FNIM07-01.htm

vii www.osteoporosis.ca/english/about%20osteoporosis/nutrition/vitamin%20d/default.asp?s=1 The Canadian Osteoporosis Society's recommendation is soon to be updated; refer to www.osteoporosis.ca.

viii www.cancer.ca/ccs/internet/mediareleaselist/0,,3172_1613121606_1997621989_langId-en.html

ix www.dermatology.ca/media/position_statement/vitamin_d.html

Vitamin D in Canadian foods and supplements

Food sources of vitamin D

As there are too few natural dietary sources of vitamin D available to realistically compensate for low endogenous synthesis, fortification of milk and margarine is mandated in Canada.[8] Main food sources of vitamin D include fortified cows milk, infant formula and margarine, as well as natural sources from salmon, eggs and beef. Additional products are fortified soy beverages, rice beverages and orange juice, and yogurt made from fortified cows milk (Table 3).

> **The two types of dietary sources of vitamin D**
> - **Vitamin D_2** (ergocalciferol)—present in a few plant sources such as mushrooms and fortified plant beverages
> - **Vitamin D_3** (cholecalciferol)—from animal-based foods; the form found in most food sources and supplements in Canada.

Table 3: Common Dietary Sources of Vitamin D*,[x]

Food (amount)	Approximate Vitamin D (IU)
Cod liver oil (1 tbsp)	1360
Salmon (100 g cooked)	272–904
Canned fish (tuna, sardines, salmon) (100 g)	80–780
Pasteurized fortified cows milk (250 ml)	88
Fortified plant beverages, including soy, rice or orange juice (250 ml)	80
Yogurt made with fortified cows milk (100 g)	25
Egg yolk (1)	25
Beef (100 g cooked)	25
Margarine (1 tsp)	25
Shiitake mushrooms, dried (10 g)	166 (vitamin D_2)
Infant vitamin D syrup/drops (1 ml)	400
Infant formula (250 ml)	100

*Source: Canadian Nutrient File (CNF), 2007b. Nutrient content varies by source, species and other factors. www.hc-sc.gc.ca/fn-an/nutrition/fiche-nutri-data/cnf_aboutus-aproposdenous_fcen-eng.php.

Sources for the breastfed infant

Sources of vitamin D typical to the exclusively breastfed infant's diet include small amounts in the mother's milk, and vitamin D drops/syrup.[xi] Upon weaning or through introduction of complementary foods, other sources of vitamin D include fortified cows milk or formula and possibly margarine. Consuming ~1 L of formula or cows milk upon weaning would provide ~400 IU vitamin D daily which would not be excessive.[1] However, most infants do not consume this much milk and should receive a supplement until such volume is achieved. Other vitamin D containing foods such as egg yolks or salmon are not usually consumed by infants less than 9 months of age. Other products that include vitamin D, such as fortified soy and rice beverages and yogurt made from fortified cows milk, also are not typical to the infant diet.

Sources for children and adults

An older child or adult who drinks 2 cups of fortified milk or fortified soy beverage plus eats a 3-oz serving of salmon a week would meet the AI recommendation of 200 IU/d.

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[x] The CNF is incomplete for vitamin D and does not include many foods consumed by indigenous peoples. Health Canada is presently working to reduce this barrier to assessment of vitamin D intake from foods. (Personal communication, February 2008).

[xi] Cod liver oil may also be used; however, the vitamin A content should be considered due to the risk of toxicity at sufficiently high levels.

Inclusion of 2 cups of fortified orange juice and regular consumption of eggs and beef would approximately double this to 400 IU/d. However, many adults do not consume fortified orange juice and do not regularly eat fish. While beef and eggs are consumed more often, they typically provide <40 IU/d of vitamin D.[xii] In attempts to elevate vitamin D intakes through less commonly consumed foods, the energy and nutrient balance accompanying such high intake of juice, for example, would have to be considered.

This suggests that if the North American recommendation for vitamin D is increased to >200 IU/d, the food supply will require modification to meet the needs of vitamin D status without jeopardizing other aspects of a healthy diet. Otherwise reliance on supplements to achieve higher intakes of vitamin D must be reinforced through careful education of health care professionals and the public. For example, Canada's Food Guide now includes a recommendation for those over the age of 50 years to take a daily supplement of 400 IU in recognition that vitamin D needs are higher than can typically be obtained from food.[4]

Supplements in Canada

For any individual not able to meet vitamin D requirements through food, reliance on supplementation is routine. In Canada, pediatric and adult formulations contain variable amounts of vitamin D, suggesting that the brand names of vitamins should be solicited when conducting dietary assessments and when advising individuals or health care professionals about supplementation. In addition to multivitamin sources of vitamin D, supplements containing only vitamin D at various dosages exist and can range from 200 IU to 1000 IU per tablet. For example, most multivitamins contain 400 IU per tablet, while vitamin D supplements are typically 200, 400 or 1000 IU per tablet. For a quick reference of vitamin supplement contents, refer to the Health Canada Drug Product Database.[xiii]

Vitamin D metabolism

Vitamin D can be obtained through endogenous synthesis upon skin exposure to UVB (290–310 nm) or through foods. Upon exposure of skin to UVB, 7-dehydrocholesterol is converted to precholecalciferol, which in turn is isomerized to cholecalciferol (vitamin D_3).

- In countries above 40°N (including Canada) or below 40°S, during the winter months UVB radiation is not strong enough to elicit endogenous synthesis.[9] Typically it is assumed that endogenous synthesis can only occur from April to October;[9] however, regions in the far north or south likely do not accommodate endogenous synthesis in spring or fall, since UVB is reduced as a result of the zenith angle and the atmosphere, in addition to cold temperatures that necessitate warm clothing and thereby preclude exposure. In addition, individuals who are not able to be outdoors are vulnerable year-round. Both groups will not meet the body's requirements for vitamin D unless regularly consuming a dietary source.
- The skin pigment melanin can reduce photosynthesis of vitamin D by 50-fold, placing individuals with darker skin at higher risk for vitamin D deficiency.[10] This is a limiting factor for many people in multicultural Canada.

[xii] Source: Gray-Donald K, Johnson-Down L. *Analysis of Canadian Community Health Survey Data on Food and Nutrients. Report to the Canadian Beef Council*, 2007.

[xiii] Health Canada Drug Product Database: www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

- Age is also of relevance to vitamin D status of Canadians since age limits endogenous synthesis of vitamin D[11] and Canada has a rapidly aging population. It is estimated that by 2041, nearly 25% of the Canadian population will be over the age of 65 years, which represents 9.4 million individuals.[12]
- Sunscreen containing a sun protection factor (SPF) of 8 or greater also suppresses endogenous synthesis of vitamin D;[10] this includes products designed for regular outdoor activity and for children as well as cosmetic products such as facial foundations.

Factors that reduce synthesis of vitamin D
-latitude
-limited time spent outdoors
-skin pigment
-age
-sunscreen / clothing

How the body handles vitamin D

After entry into the circulation whether through endogenous synthesis or through foods, vitamin D_3 can be transported free or bound to the vitamin D binding protein (DBP). This protein is synthesized by the liver[13] and not only carries vitamin D_3 within the blood and extends its half-life, but also binds to other forms including vitamin D_2 obtained from food. Approximately 75% of vitamin D is removed from circulation by the liver upon each pass for further metabolism to 25(OH)D (calcidiol).[14] Vitamin D from all sources is hydroxylated to 25(OH)D by the liver and released into circulation where it again binds to DBP, but with stronger affinity.[13]

Relative potency of vitamin D isoforms

Vitamin D_3 is estimated to be 1.7 to 3 times more potent than vitamin D_2 based on the rise in serum 25(OH)D in adults (9, 10). One recent study suggests that if the supplement is taken daily, both isoforms equally maintain 25(OH)D.* Such relative potency studies have not been conducted in infants, children or pregnancy/lactation and thus the optimal intake of either isoform to support a theoretical optimal concentration of 25(OH)D is uncertain. Nonetheless, vitamin D_2 likely has a shorter half-life since it does not bind as readily to the plasma carrier protein, vitamin D binding protein (DBP) (11). Thus, if vitamin D_2 is not consumed daily, it might not be effective in sustaining adequate status in the longer term.

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*e-pub ahead of print: http://jcem.endojournals.org/cgi/rapidpdf/jc.2007-2308v1

Because of its lipid solubility, vitamin D can also be sequestered in adipose tissue. Individuals who are obese have 20% lower vitamin D status after accounting for exposure to UVB and diet;[15] thus, it appears that obesity is a risk factor for having low vitamin D status. Since 34% of Canadian children are overweight (26% overweight and 8% obese)[16] and 15% of adult Canadians are obese,[17] this reality is an important consideration in the study of vitamin D.

Functions of vitamin D

The most widely understood function of vitamin D is in calcium homeostasis, but knowledge of emerging roles in other tissues is rapidly evolving. The active form required in physiology is $1,25(OH)_2D$ (calcitriol). Synthesis of $1,25(OH)_2D$ from 25(OH)D occurs in the kidney for the purpose of calcium homeostasis and in other tissues for non-calcemic functions.[18] This conversion is tightly regulated by parathyroid hormone (PTH) in response to serum calcium and phosphorus levels. Serum PTH concentrations are inversely related to 25(OH)D serum levels.

When the blood calcium level falls, PTH is released to promote hydroxylation of 25(OH)D to $1,25(OH)_2D$. Both PTH and $1,25(OH)_2D$ mobilize calcium from bone and enhance

absorption of calcium from the diet and glomerular filtrate. Vitamin D and PTH follow similar circannual rhythms, with PTH fluctuating 20% above and below the annual mean in winter and summer, respectively.[19] It is now accepted that PTH plateaus within the normal range when 25(OH)D concentration is over 50–80 nmol/L regardless of seasonality.[7] This plateau of PTH likely is positively associated with bone accretion since a 25(OH)D concentration >75 nmol/L is associated with higher bone mass.[20] Changes in 25(OH)D are followed 1 month later by changes in PTH, and changes in bone resorption follow changes in PTH by 1 to 2 months.[21] Elevated PTH levels characteristically seen in individuals with inadequate vitamin D status can result in the long latency disease of osteoporosis,[22] but might more readily associate with acute complications such as tetany and myopathy. In infants and children, vitamin D deficiency causes rickets and in adults it causes osteomalacia. A high PTH can also result from low dietary calcium, making the study of vitamin D status, PTH and calcium homeostasis complex.

In addition to calcium homeostasis, vitamin D in its active state ($1,25(OH)_2D$) has the capacity to modify cellular activity, cell differentiation and proliferation,[23, 24] and is thus said to have a pleiotropic role in physiology and health. Vitamin D receptors have been reported in all organs (e.g. immune cells, brain, heart, pancreas, intestine), suggesting functionality in these tissues.[25] When vitamin D receptors bind $1,25(OH)_2D$, the complex heterodimerizes with the retinoid X receptor, which in turn binds to the vitamin D response element of genes. Depending on the cell type, protein transcription is regulated in response to $1,25(OH)_2D$.

Assessing vitamin D status

Serum 25(OH)D reflects vitamin D derived from foods or endogenous synthesis and thereby reflects the cumulative vitamin D status.[1] There are a variety of assays available.[26] Regardless of the assay, it is widely accepted that vitamin D deficiency in adults (Table 4) is diagnosed when serum 25(OH)D is <15 ng/ml or <37.5 nmol/L.[1] These levels are consistent with the signs and symptoms of osteomalacia, tetany and myopathy.[1] For infants and children, a vitamin D deficiency is defined by a serum 25(OH)D <11 ng/ml or <27.5 nmol/L.[1] These levels are consistent with the signs and symptoms of rickets.[1]

While the DRI report does not suggest an optimal serum 25(OH)D, hypervitaminosis D is defined by the range of 400 to 1250 nmol/L.[1]

Table 4: Definition of Vitamin D Status Based upon Serum 25(OH)D (nmol/L)

Category of Vitamin D Status	Institute of Medicine and Health Canada[1]		Canadian Paediatric Society[5]
	Infants and Children	Adults	Infants and Pregnant/Lactating Women
Deficient	<27.5	<37.5	<25
Insufficient	ND	ND	25–75
Optimal	ND	ND	75–225
Pharmacological	ND	ND	>225
Potentially toxic	ND	400–1250	>500

ND: Not defined

The suggested target for optimal 25(OH)D in adults is widely accepted as at least 75 nmol/L, as suggested by a panel of international experts.[7] This value is based on dose–response studies of vitamin D supplementation in men and women where a plateau in PTH was observed.[27, 28] There are many examples of studies in adults supporting this optimal range, six of which are well summarized by the panel.[7] The panel suggests that after correction for different assays, 75 nmol/L is the consensus concentration at which PTH plateaus in adults <70 years of age.[7]

Whether these concentrations are appropriate for other life stage groups has not been proven. Caution is warranted in using these values for infants and children since dose–response studies have not been forthcoming. Particularly in infants and young children under 7 years of age there are scant data upon which to establish such criteria. There is, however, a growing body of information indicating that other life stage groups can achieve a serum 25(OH)D concentration of 75 nmol/L. Similar cut-off values have been recently proposed for infants and pregnant women by the working group of the Canadian Paediatric Society[5] (Table 4).

Consequences of vitamin D deficiency

Skeletal consequences

Rickets—Because of the pleiotropic actions of vitamin D,[23,24] a deficiency is associated with not only reduced fetal mineralization,[29, 30] but also reduced bone growth[31] and in some cases defective bone modeling resulting in congenital rickets.[32] Even if congenital rickets is not evident at birth, such deficiency is associated with a higher incidence of infant morbidity, including symptomatic hypocalcemia that may present as seizures,[33, 34] hypoplastic lungs presenting as respiratory distress syndrome,[32, 35] and hypotonic musculature.[35] Vitamin D status positively relates to APGAR scores (an assessment of the infant's Activity, Pulse, Grimace, Appearance, and Respiration),[36] suggesting a role in critical vital signs. Thus, correction of maternal vitamin D deficiency has vast implications for fetal and neonatal health outcome.

Vitamin D deficiency in mothers[37-42] and infants[38-44] is evident throughout the world, covering a wide range of geographic regions and cultures. Vitamin D deficiency has caused congenital rickets[32, 35] and re-emergence of vitamin D dependent rickets in infants.[45-49] According to the recent pediatric surveillance assessment of rickets in Canada, an estimated 2.9 cases per 100,000 occur in infants ranging from 2 weeks to 6 years of age.[50]

Early life programming of bone mass—Overall, early life nutrition, both *in utero* and postnatally through breast milk and vitamin D, is documented to have long-lasting affects on bone. Maternal vitamin D status in the third trimester of pregnancy positively associated with bone mass in the offspring at 9 years of age.[51] Optimal nutrition during infancy, including breastfeeding[52,53] and vitamin D supplementation,[54] is also linked to higher bone mass in children. The growing evidence that early life nutrition programs later bone health,[55-57] combined with growing evidence that vitamin D status is compromised through pregnancy and childhood, places many Canadians at risk for poor bone health.

Children—Canadian data demonstrate that maximal calcium accretion is achieved at the age of 12.5 years for girls and 14.0 years for boys.[58] Bone mass attained early in life is considered the most important determinant of bone health later in life.[59] Peak bone mass is defined as the highest bone mass achieved and in Canada this is attained somewhere between 25 and 40 years of age.[60] Thus, childhood (birth to 18 years of age) accounts for most of the biological window whereby bone mass is developed. Recent studies[61, 62] underscore the importance of vitamin D status to support bone mineral accretion.

Young adults and aging—The most well-studied age group with respect to vitamin D nutrition is adults, with emphasis on those over 65 years of age. Vitamin D supplementation trials have shown that higher intakes of vitamin D associate with higher vitamin D status, which is associated with better bone mass, tooth retention, fewer falls and some improvements in physical ability.[3] This research area is well reviewed in the NIH systematic review[3] and thus not detailed herein. From that review, however, the majority of studies have used 800 IU as the upper end of the dose–response investigation.[3]

An area requiring further study is the amounts of vitamin D required to optimize peak bone mass during the consolidation years; that is, in young adults 18 through 40 years of age.

Reproductive women—Bone loss in women with vitamin D deficiency during pregnancy and lactation may also be a risk factor for osteoporosis. It is estimated that a woman can lose up to 10% of her bone mass during lactation,[63-68] with greater losses evident in women who breastfeed longer.[63] Notably, trabecular bone mass is lost in the femoral head and lumbar spine with lactation.[69] Yet, it seems in some studies that lactation does not have long-term negative effects on the skeleton,[70-72] and might in fact present an opportunity to increase bone mass or protect against osteoporotic fracture at trabecular sites.[73]

While vitamin D status of a woman is not expected to be compromised by pregnancy or lactation to a great extent (i.e. small amounts are transferred to the infant), women with low vitamin D status may not recover as well from the demands of pregnancy/lactation with respect to bone mass. It is reasonable to expect that bone health of mothers will benefit from improvements in vitamin D status. This speculation is highly supported by recent work in lactating women in which high dosage vitamin D supplementation (2000 to 4000 IU/d for 3 months) had a positive affect on 25(OH)D concentrations[74] into the range associated with optimal bone mass.[7] In another study, women receiving 400 IU/d vitamin D plus 1 g of calcium readily recovered mineral losses during pregnancy and lactation after an equal period of weaning.[64] Thus, the benefits of lactation on bone mass might best be realized in association with optimal vitamin D status.

Non-skeletal consequences

Non-skeletal chronic diseases that might originate from vitamin D deficiency and the genomic response include cancer, multiple sclerosis, schizophrenia and diabetes.[75] Epidemiological studies reveal that the prevalence of these diseases is greater as latitude increases, suggesting that lower exposure to UVB radiation and associated decreases in vitamin D synthesis may play a role in their pathology. However, the associations between vitamin D exposure and development of these chronic diseases are not yet as convincing as they are for bone.

Cancers—Many epidemiological studies suggest that vitamin D is important in cancer prevention. Cancers associated with vitamin D deficiency include non-Hodgkin lymphoma,[76] leukaemia,[77] and breast cancer.[78] Additionally, glioblastoma is most frequently diagnosed in a winter month[79] and the incidence of brain tumours in adults is higher in those born in the winter.[80] These studies were not conducted in a Canadian population. Intervention studies show that for men, higher vitamin D status is associated with slower progression of prostate cancer.[81] Vitamin D in a case–control study shows that higher intakes and status are associated with lower risk of breast cancer in women.[82] These two studies were conducted in a Canadian population.

Immunity and brain development—Vitamin D is also proposed as a critical neuroactive substance as it has wide-ranging effects in brain including induction of nerve growth factor.[83] The possible etiology of different cancers might be rooted in development and function of the immune system.[23, 75, 84] These findings suggest that low maternal vitamin D has important ramifications for the developing immune system and brain. However, these studies were done at extreme vitamin D deficiencies, and the long-term effects and a clear link to learning have yet to be determined.

Multiple sclerosis and schizophrenia—Canada is leading the way in describing the role of vitamin D in multiple sclerosis,[85] while Australian research shows that during the winter months with less UVB, there is a 7–10% increase in the number of people born with schizophrenia.[86]

Type 1 diabetes—Epidemiological studies examining early vitamin D supplementation and the risk of type 1 diabetes[87-90] suggest vitamin D protects against development of this autoimmune disease.[84] More recent intervention studies are lacking and studies showing that optimal maternal vitamin D status in pregnancy reduces the incidence of type 1 diabetes in the child are also lacking. Vitamin D status is also associated with glucose metabolism and insulin sensitivity index in adults even after correcting for age, gender and BMI.[91] This was confirmed in a secondary analysis of vitamin D supplementation originally designed to test for bone health.[92] In a short one-month randomized clinical trial (RCT) using 1332 IU/d vitamin D in adults with type 2 diabetes, the initial secretion of insulin following an intravenous glucose challenge was significantly elevated by 34% accompanied by non-significant reductions (24%) in insulin resistance.[93] Even though 25(OH)D concentrations increased over the month (124), longer durations are required in adults to arrive at optimal concentrations of >75 nmol/L (24) that are thought to be required for glucose homeostasis.[94]

GDM and type 2 diabetes—As noted earlier, obese women are at higher risk of vitamin D deficiency.[95] Coincidently they are also at heightened risk for developing gestational diabetes mellitus (GDM) if they do not already have type 2 diabetes. A recent report shows that severe vitamin D deficiency (<12.5 nmol/L) is more commonly observed in women with GDM compared to the controls (22 nmol/L) and that vitamin D status strongly associates with an index of insulin resistance.[96] Even glucose intolerance was associated with intermediate deficiency (18 nmol/L). These low values within the realm of deficiency demonstrate a dose-effect for different health outcomes, again implying that deficiency should be eradicated to promote both maternal and fetal health. The limitation with readily

drawing conclusions from this study, however, is that the women with GDM also had a higher BMI than the control women. However, in a non-pregnant state, vitamin D status was strongly related to the insulin sensitivity index even after correcting for age, gender and BMI.[91] Thus, the relationship between vitamin D and GDM might not necessarily be confounded by BMI and requires clarification. Pursuing such a potential intervention is important not only for prevention of GDM and the associated pregnancy complications, but also because of the possibility of reducing susceptibility to development of type 2 diabetes postpartum.[97]

Preeclampsia—Women are vulnerable to complications associated with vitamin D deficiency in pregnancy. Preeclampsia (PE) is a pregnancy disorder characterized by maternal hypertension, proteinuria, edema, and fetal growth restriction. Epidemiological studies and clinical studies demonstrate alterations in maternal calcium metabolism in PE and relationships to dietary calcium intake.[98, 99] In this context, PE is characterized by lower serum calcium concentration,[100] hypocalciuria,[101, 102] raised PTH concentration[103] and decreased plasma 1,25(OH)$_2$D concentration[102] in the mother and low birth weight in the offspring. All of these clinical symptoms also are associated with vitamin D deficiency, implicating vitamin D in the development of PE. This speculation is supported by a case–control study that reported 25(OH)D values <50 nmol/L were associated with a two-fold risk of developing PE, whereas 25(OH)D <37.5 nmol/L (deficient) was associated with a five-fold elevation in the odds of developing PE.[104] This association was independent of race, season, BMI and education. Interestingly, 93% of the women took a prenatal supplement. However, based on the Health Canada Drug Product Database,[xiv] this would be <400 IU/d on average and not enough to provide for optimization of vitamin D status.

In women given calcium and vitamin D supplements, the incidence of PE was reduced from 16.9% to 10.9%.[105] However, RCT are few in the area of vitamin D and PE. Large-scale RCT are required to establish if optimization of vitamin D throughout pregnancy is effective in reducing the incidence of pregnancy-induced hypertension and PE. The value of such a study might translate into generations of health since vitamin D status in pregnancy is now reported to be a predictor of PE later in reproductive years.[106] Improvements in vitamin D function through 1,25(OH)$_2$D treatment is also proposed to reduce spontaneous abortions.[107]

[xiv] www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php

Limited information is available on Canadians' vitamin D intake and status.[xv] Many groups appear to be meeting the AI for vitamin D, yet deficiency is evident. The cause of vitamin D deficiency in many Canadians appears to be rooted in inadequate endogenous synthesis combined with intakes that are not sufficient alone to support vitamin D status. Optimal intakes have yet to be defined; however, if recommended intakes are increased, many people will be unable to achieve higher intakes unless food fortification policy and supplementation practices change.

Infancy

Vitamin D intake and status

Assessment of vitamin D intake by infants in Canada is limited. Data from the Canadian Community Health Survey (CCHS 2.2) are not yet forthcoming. The few available studies suggest low use of supplements and problems with transition to weaning foods.

From the 1990s it was apparent that in northern Canada, most infants were born with serum 25(OH)D <30 nmol/L.[108] It was estimated that up to 80% of the non-white infants were at risk for vitamin D deficiency.[108] More recently in Manitoba, 36% of infants from white or non-white parents were found to be deficient in vitamin D at birth, defined as a serum 25(OH)D <27.5 nmol/L.[30] In a northern Manitoba community, 43% of infants 3 to 24 months of age had serum vitamin D levels below the normal range.[109]

Health issues

Among the 2.9 cases of rickets per 100,000 in Canada among those aged 2 weeks to 6 years,[50] the majority were characterized by darker skin pigmentation and lack of vitamin D supplementation. Even some infants fed formula will develop rickets,[34] presumably since maternal–fetal transfer of vitamin D is inadequate and consumption of only 200 IU/d (0.5 L of formula) is not enough to compensate for any deficiency acquired *in utero*. Similarly, from 1990 to 1998 in the United States, 9 cases per million of children were estimated to have rickets.[110] The common factor among all cases was that they were breastfed term infants for whom supplementation practices were questionable.

Solutions for improving vitamin D nutrition in Canadian infants

It is important to provide evidence to support an oral dosage of vitamin D for optimal bone health outcomes, including safety. Yet very few dose–response studies exist for vitamin D supplementation in infancy. Current recommendations have not been rigorously tested using dosages at and above the suggested intake values. Three randomized trials (RT) were all conducted at latitudes similar to Canada, but only in infants ≤6 months of age. There are no RCT for vitamin D_3, as is used in Canada, at dosages beginning at 400 IU and extending to 800 IU and above as recommended by Health Canada[2] and the Canadian Paediatric Society.[5] Two RCT are currently underway, both beginning at one month of age: one in Canada with dosages ranging from 400 to 1600 IU[xvi] and the other in the USA using 200 to 600 IU.[xvii]

[xv] More knowledge about the vitamin D status of Canadians must await the planned assessment in the Canadian Community Health Measures survey; data dissemination is expected in late 2009 (www.statcan.ca/english/concepts/hs/measures.htm).

[xvi] www.clinicaltrials.gov; Identifier NCT00381914

[xvii] www.clinicaltrials.gov; Identifier NCT00494104

Childhood

Vitamin D intake and status

Assessment of the vitamin D intake of Canadian children is limited, but several studies (published and unpublished) have included dietary assessment with either direct (amount of vitamin D/d) or indirect (servings of milk) evidence of vitamin D intake.[111-118] The Canadian data are very similar to those in the USA.[119] Overall, most North American children seem to meet the current recommendation of 200 IU/d. Groups at higher risk for not achieving adequate intake include teenage girls[119] and First Nations children.[115]

Children in Canada do not appear to have serum 25(OH)D levels consistent with the hypothesized optimal concentration (i.e. 75–80 nmol/L).[xviii] In fact, in all existing reports a significant proportion have 25(OH)D consistent with vitamin D deficiency.

Health issues

Reports of rickets that include children over 1 year of age have been published for many years,[48, 49, 120] and the reported prevalence of rickets in Canada (2.9 cases per 100,000) includes those ranging in age from 2 weeks to 6 years.[50] The risk factors for children are the same as for infants (aside from breastfeeding without supplementation). Reports of rickets in older children (i.e. >6 years old) are lacking in Canada, suggesting that either intakes or endogenous synthesis are sufficient to prevent severe deficiency.

Solutions for improving vitamin D nutrition in Canadian children

During the winter months in Canada, in the absence of sunlight or safe exposure to UVB, it is unclear how much oral vitamin D is required to achieve and maintain optimal 25(OH)D levels in children. Overall, research conducted in other countries suggests that if 75 nmol/L is adopted as the optimal target for all ages, the current AI of 200 IU/d seems inadequate. It is more likely that RCT designed to test for the dietary intake required to optimize 25(OH)D will be successful in using dosages over 200 IU/d. Daily dosages of vitamin D_2 and D_3 isoforms greater than 200 IU require testing.

Young adulthood (18–50 years of age)

Vitamin D intake and status

There are few reports regarding vitamin D intake of young adults in Canada. One study shows that women frequently do not achieve the 200 IU/d AI,[121] and some other reports echo this low intake. Based on milk intakes from the CCHS 2.2 dataset[122] and the Food Habits of Canadians studies,[123] most men and women do not consume even 2 servings of milk and thus vitamin D intake is most likely <200 IU/d.

More reports exist on the vitamin D status of healthy adults than on their dietary intake. For example, in Toronto, deficiency is prevalent in 14.8% of white women and 25.6% of non-white non-black women, even if they consume 200 to 400 IU of vitamin D daily.[121] During the winter months, the prevalence was not significantly affected by dietary or supplemental vitamin D intakes at values similar to the AI of 200 IU/d (5 µg/d).[121]

[xviii] Further research is required to prove whether 75–80 nmol/L is the optimal target for 25(OH)D levels in children.

Health issues

Most health outcomes related to vitamin D are chronic in nature and the consequences of the vitamin D deficiency observed in Canada are not clear. Much of the research regarding vitamin D deficiency has focused on bone health and osteoporosis. More recently, vitamin D deficiency has been associated with other chronic diseases, but the association is not yet as convincing. Canadian research related to multiple sclerosis,[85] prostate cancer[124] and breast density[82, 125, 126] suggests that individuals with higher 25(OH)D have better odds of achieving improved health.

Solutions for improving vitamin D nutrition in Canadian men and women 18–50 years of age

The mandated food fortification of milk and margarine in Canada[8] makes significant contributions to vitamin D status. Several reports also show that many Canadians consume vitamin D supplements. To achieve 25(OH)D levels of 75 nmol/L, Canadian data suggest that 200 IU/d is inadequate and that intakes of 1000 to 4000 IU/d might be required in some individuals during the winter months.[28] Selection of foods containing vitamin D is important and supplementation is required during the winter.

Reproduction: maternal–fetal, maternal–infant

Vitamin D intake and status

National surveys on vitamin D intakes from diet and supplements in this group are lacking. The few studies available suggest that many women do not take the recommended supplements during pregnancy and have 25(OH)D in the deficient range.[30, 108, 109] A recent review paper summarizes the literature on vitamin D status in pregnancy throughout the world.[127] That review, covering the period 1966–2002, revealed that 35 of 76 (46%) reports included women with 25(OH)D concentrations <35 nmol/L; the majority of reports emanated from Europe and the UK. Thus, vitamin D deficiency during pregnancy is common in industrialized nations.

The total amount of vitamin D transferred from mother to fetus is thought to be small relative to maternal stores.[1] Changes in vitamin D status over pregnancy are more likely attributed to reductions in both endogenous and exogenous sources rather than a high demand for fetal vitamin D requirements. As two of the factors that limit endogenous synthesis, dark skin pigmentation or concealing clothing yield higher prevalence of deficiency in infants (63 vs 16%).[128] In Winnipeg, about 75% of non-white and 30% of white pregnant women were vitamin D deficient, defined as serum 25(OH)D <37.5 nmol/L;[30] sampled 1 to 2 days postpartum, only five (10%) had a 25(OH)D concentration >75 nmol/L.[30] In another report, up to 80% of women and their infants were at risk of vitamin D deficiency if they were non-white.[108] Not taking supplements can exacerbate this problem. Infants of mothers with these characteristics are often vitamin D deficient by 3 months of age.[129] Even in warmer countries closer to the equator, infants of darker skin are frequently diagnosed with rickets.[46, 130]

As noted earlier, low 25(OH)D might also be related to maternal weight.[95] However, supplementation is more likely to be important than screening on the basis of BMI.[131]

Health issues

Within Canada, the consequences of low 25(OH)D in pregnancy are not clear. It is assumed that the consequences would be the same as those observed in other countries and

for Canadian women in general. These include bone loss, tetany, gestational diabetes, and preeclampsia.

Solutions for improving vitamin D nutrition in Canadian women during reproduction

The ongoing deficiency in pregnant women needs to be resolved in view of the early life programming hypothesis and recent evidence linking vitamin D status to pregnancy outcome for the mother as well. It is clear that dietary sources of vitamin D and *de novo* synthesis in today's environment are not enough to support optimal vitamin D status (potentially 75 nmol/L[132]) in maternal–infant populations in Canada.

Whether higher intakes in the order of 1000 IU/d would be beneficial to deficient populations is not clear without further research. Nonetheless, 400 IU in addition to a normal diet appears safe and able to elevate 25(OH)D well into the proposed target range of >75 nmol/L. The 400 IU of vitamin D would be possible with most pregnancy supplements. The challenge to obstetric care is to find approaches that ensure pregnant women regularly select vitamin D containing foods and rigorously practice vitamin D supplementation.

There are no clinical trials or RT of vitamin D intake in pregnant or lactating women in Canada. However, trials exist from other countries from which we can gain appreciation of the relationship between vitamin D intake and status. The few RCT of vitamin D supplementation in pregnancy that exist were conducted in the 1980s; debate continues regarding optimal intakes or supplementation levels as disagreement exists among studies.

For pregnancy—In a 2001 Cochrane Database systematic review,[133] only two[134, 135] trials reviewed at that time met inclusion criteria. Both trials were based on the administration of 1000 IU/d supplement of vitamin D_2 in the third trimester. These studies reported elevated maternal 25(OH)D, but one trial[134] showed improved birth weights while the other[135] showed reduced birth weights in the intervention groups relative to the control groups. Results of seven other trials,[136-142] some conducted since the systematic review, do not agree in regard to elevations in 25(OH)D at a specific dosage of vitamin D during pregnancy. This discrepancy would suggest that other factors such as geographic location and exogenous synthesis, endogenous stores of vitamin D and supplement compliance contributed to the outcome.

Newer trials are underway to establish if 1000 IU/d is sufficient to achieve and maintain vitamin D status in pregnancy.[xix] While clinicians await the results of RCT, they should be aware that the theoretical optimal concentration of 25(OH)D of 75 nmol/L can be achieved in pregnancy.

For lactating women—There are four RT of vitamin D supplementation, with dosages ranging from 1000 IU to 6000 IU/d. Two studies are from the USA,[143, 144] one from Finland[145] and one from the United Arab Emirates.[146] From these studies, it seems that 4000 IU/d is required to elevate maternal 25(OH)D into the 75 nmol/L range[143, 145] and that women with darker skin pigmentation consuming 2000 IU for 3 months do not fully optimize vitamin D following a deficiency.[146] Information regarding 25(OH)D in the infant also shows values of ~75 nmol/L when the mother consumes 2000 IU/d.[143, 145] It is likely

[xix] www.clinicaltrials.gov; Identifier: NCT00292591

for this reason that the recent recommendation by the Canadian Paediatric Society is set at 2000 IU for lactating women.[5] However, it is more effective and prudent to supplement the infant directly, particularly if the mother is vitamin D deficient as correction of maternal status might take too long to provide sufficient transfer through breast milk.

Aging and advanced aging (50 years of age and older)

Vitamin D intake and status

In Canada very few reports exist on vitamin D intakes in free-living individuals. First Nations women over 50 years of age and white women from Winnipeg have intakes in the order of 450 and 544 IU/d, respectively.[147] These intakes are consistent with the AI of 400 to 600 IU/d for adults over 50 years of age. Additionally, for Dene and Inuit, intakes approximate 316 to 1000 IU/d from traditional and market foods.[115] Institutionalized elderly have low dietary intakes of vitamin D of ~450 IU/d.[148] One study shows that novel foods for dysphagia management in long-term care improve vitamin D intakes to approximately 600 IU/d.[149]

Reports exist regarding vitamin D status, but the relationship with diet remains unclear. For example, in Canada, deficient vitamin D status is observed in at least one season in 34% of Calgary residents ~64 years of age,[150] but determining the relationship between supplement use and vitamin D status was not possible since use of supplements was an exclusion criterion. Some data exist for institutionalized elderly and are suggestive of low vitamin D status[151] despite a controlled feeding environment. However, the state of community-dwelling seniors is far less clear.

Health issues

As is the case for younger Canadian adults, the consequences of the vitamin D deficiency observed among older Canadians are not entirely clear. Even for osteoporosis and fractures, a direct linkage to vitamin D status in Canadians is not available.

Solutions for improving vitamin D nutrition in aging Canadian adults

Unless food fortification policy changes, aging adults will not be able to achieve intakes of 600 IU/d and higher in support of year-round optimal vitamin D status. The new Canada's Food Guide recommends a supplement of 400 IU/d for adults over the age of 50 years.[4] Supplementation trials in Canadians over 50 years of age show that both 600 and 4000 IU/d supplemental dosages given over a 6-month period elevate 25(OH)D to >75 nmol/L.[152] However, for those over 70 years of age, the suggested target for 25(OH)D might be higher and thus higher intakes would be required. From the meta-analysis component of the NIH systematic review of vitamin D,[3] it appears that every 100 IU elevation in vitamin D intake increases serum 25(OH)D by 1 to 2 nmol/L. If this is the case and if 75 nmol/L is the minimum optimal target, Canadians deficient in vitamin D (i.e. serum level <37.5 nmol/L) would require anywhere from 3750 IU/d to 7000 IU/d. Whether such dosages are warranted in Canada requires further study. Once deficiency is corrected, lower intakes might possibly provide coverage in the longer-term.

Implications

General implications

The underpinning philosophy of dietary recommendations is to meet the needs of the majority of people. When the IOM published the DRIs for vitamin D in 1997, for most age groups the AI for vitamin D was set at 200 IU/d.[1] The AI pertains to dietary intake only, recognizing that exposure to sunlight may not be the best approach to ensuring adequate vitamin D status of populations as this can be dependent many factors.[1, 2] Other institutions and associations have put forth recommended intakes for vitamin D ranging from 400 IU/d for infants to 2000 IU/d for pregnant and lactating women.

The state of vitamin D nutrition in Canada suggests that vitamin D intakes are close to the AI across all ages, but that vitamin D deficiency is very common among all groups studied. The implication of these observations is that Canada's current health policy, food fortification policy and food supply require updating if optimization of vitamin D status is to be achieved. Additionally, the AI is most likely too low to prevent vitamin D deficiency in most individuals, regardless of ethnicity, although many ethnic groups have high prevalence of deficiency (as high as 100% in some studies). While newer recommendations exist for Canadians, these are not yet all part of Health Canada's policy update. Only the 400 IU/d for infants has been accepted by Health Canada.[2] Furthermore, if a serum 25(OH)D of 75 nmol/L is accepted as the target indicative of optimal vitamin D status, further research is required to establish how much daily dietary vitamin D is required to support healthy outcomes.

Establishment of public policy recommendations is critical to ensuring safety for the public at large. With the expanse of vitamin D deficiency, the risks of updating the recommendations for pregnant women without multiple sound intervention trials might be smaller than the risk of not correcting vitamin D deficiency. Not only are there acute and chronic implications for maternal health, but also the consequences of missing critical windows for programming of fetal health and prevention of chronic disease may manifest as an increased burden of chronic disease.

Lastly, the implication of not clarifying the best dietary intake is that the public will receive a multitude of recommendations and possibly not have confidence in dietary advice. Many will self-medicate with respect to vitamin D without sound knowledge or medical supervision, and will thus be less likely to achieve healthy outcomes.

Implications for doctors and other health care professionals

Since health policy is not readily altered due to the responsibility to ensure public safety and since many knowledge gaps exist, the responsibility of medical and other health care professionals to know the facts about vitamin D is most important. To date, there are few reports of the practices of Canadian health professionals with regard to vitamin D nutrition, and these only deal with adult clients. From other countries, it seems that vitamin D intakes in children can be improved with counseling. For example, according to Christie et al. in Arkansas, vitamin D intake in children with allergies is higher with counseling than without.[153] This research group recommends that children with diagnosed food allergy be counseled yearly and that their annual nutritional assessments include the status of vitamin D nutrition. Two other American references report that physicians and nurse practitioners recommend vitamin D supplements for breastfed infants less than 50% of the

time. Physicians and nurse practitioners are more likely to recommend supplements if they were either trained at a time when rickets was prevalent or have worked in geographic regions where the risk of rickets is high.[154, 155] From Finland, it seems that while health care professionals believe they educate women on giving vitamin D to their infants, most women state they have not received this information.[156] From within Canada, 75% of medical professionals are interested in vitamin D and are open to receiving more education on this topic.[157] However, current practice related to use of vitamin D in treatment of osteoporosis does not match guidelines.[158, 159]

From the above reports, it is clear that health care professionals know that vitamin D nutrition is important, but need to seek further education about current recommendations and follow these recommendations carefully.

Implications for industry

In Canada, fortification has been questioned for quality control.[160] Thus, it is in industry's best interest to prove that fortification is under high-level quality control to ensure the food supply delivers reliable sources of vitamin D. In some studies, milk products are not linked to vitamin D status in young adults in Canada,[121] while in others milk and margarine are clearly the foods with greatest impact on vitamin D status.[82, 126, 147] Newer foods on the market including orange juice have not yet been assessed for contribution to vitamin D intake and status in Canada.

For the pharmaceutical industry, this research also has implications. It is in industry's best interest to clarify the optimal dosage of vitamin D from all sources that elicits optimal outcomes including safety assessments.

Lastly, for all industry clear food labeling is critical for public acceptance of vitamin D. Whether the product contains vitamin D_3 or D_2 is important to some segments of the population, regardless of the dosage.

Implications for consumers

Ultimately, consumers are responsible for their dietary intakes and well-being. Individuals must seek education as to which foods are the best sources of vitamin D and what are appropriate serving sizes and frequencies. Compliance in taking supplements and consistency in selecting foods containing vitamin D are likely critical to achieving better vitamin D status. Consumers must seek nutritional or medical counseling to learn of the benefits of foods and supplements while ensuring safe intakes for themselves and any people for whom they are the primary caregiver. The consumer must be educated upon valid sources of nutrition information and become skilled in reading food labels.

Implications for research—knowledge gaps for Canada

The knowledge gaps about vitamin D nutrition for healthy outcomes in Canada include:

- **The cause of vitamin D deficiency**
  Is it low food sources and lack of adherence to supplementation guidelines, or is the target too low given lifestyle and health risks related to exposure to UVB?
- **The consequences of a high rate of vitamin D deficiency for all age groups and among different ethnic groups**

- **Definition of optimal vitamin D status in all age groups**
  This is critical to harmonization of the various recommended intake values and to harmonization of policy with public education.
- **Determination of optimal vitamin D intake in all age groups**
  How much dietary vitamin D from diet or supplements is required to achieve optimal vitamin D status?
- **The nature and safety of supplementation**
  Is a bolus dosage safe and effective? What is the maximum amount of vitamin D supplementation that is safe?
- **Efficacy of food fortification programs**
  Can food fortification programs safely and successfully enhance vitamin D status?

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