Vitamin D is Essential for Optimal Health: Are you getting enough?

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Revised **March 10, 2024**

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The information herein is for educational purposes only and is not to be taken as medical advice; please consult a healthcare professional for personal advice.

Fellow Canadians,

Let us make a significant improvement in our collective health and save our country billions of dollars annually by simply paying attention to our vitamin D sufficiency. Please do the following:

- Read the Abstract below and the full document if possible.
- Consider if you are vitamin D sufficient or if supplementary vitamin D is advisable for you, your family and your friends.
- Discuss vitamin D testing and sufficiency with your doctor, nurse or other healthcare providers.
- Contact the following with your vitamin D concerns: your local public health officer, provincial public health officer, provincial MP/MLA, federal MP, and any others who would benefit from your educating them.
- Request that vitamin D testing be covered by provincial health plans to help citizens take appropriate doses of vitamin D.

Abstract

Multiple studies have shown most Canadians have insufficient body levels of vitamin D (VitD, the sunshine vitamin) to ensure optimal health. The primary reason for this is inadequate exposure to sunlight's ultraviolet (UV) rays because of our northern location and indoor work, although genetics, diet, skin pigmentation, clothing, sunscreen use, air pollutants, age and other factors also contribute to VitD insufficiency.

Low VitD levels are strongly associated with a broad spectrum of diseases that hamper our enjoyment of good health such as: cancers, cardiovascular disease, diabetes, viral and bacterial infections, multiple sclerosis, dementia, other neurological disorders, and poor oral health.

The fundamental importance of VitD is demonstrated by the location of specific receptors for this essential vitamin in virtually every type of human cell, where they regulate hundreds of cellular processes to maintain good health.

Evidence now shows that the amount of VitD needed to ensure bone health is lower than that required for optimal function of its many other actions. Thus, we recommend that citizens evaluate their own VitD sufficiency and consider supplementation as necessary. While Health

Canada's suggested daily dose for bone health ranges from 400 to 800 IU/day, many researchers, doctors and health associations advocate much higher daily doses.

Evidence indicates that the Canadian population would be significantly healthier if it were to become VitD sufficient either through VitD supplementation or exposure to sunlight. Moreover, the annual savings to healthcare costs could exceed $23 billion (~6-7% of total healthcare spending in Canada for 2023, estimated to be $344 billion).

Introduction

At the Canadian Citizens Care Alliance, we believe that our healthcare "system" requires urgent attention. It does not just need more funding, it requires a change in thinking from healthcare providers and administrators. But more importantly, it requires changes in the attitudes and actions of Canadians. Instead of a sickness care paradigm, Canadian health needs to focus on wellness and health maintenance. More responsibility should be shouldered by individual citizens and less by healthcare professionals and hospitals. We will always need our professionals and hospitals, but now we need more active participation by the public, especially in light of the fact that many Canadians do not have reasonable access to doctors and nurses. At a minimum, the government must at least empower such unfortunate citizens to help themselves.

Changing this focus to individual responsibility for health maintenance is a step whose time has come. With Canada's increasing population of seniors, we see that it is also crucial to focus on prevention as well as treatment for diseases such as cancer, cardiovascular problems, diabetes mellitus Type 2 (DM2) and dementia. Society should embrace the important roles that lifestyle and nutrition play in dealing with chronic diseases. We must not miss the opportunity to decrease healthcare costs by foregoing an investment in health maintenance.

Let us consider just diabetes for a moment: some experts consider that 90% of DM2 cases could be prevented by lifestyle and nutrition intervention.[1] To make matters worse, we are trending the wrong way — the incidence of DM2 is increasing by 3.3 percent per year rather than decreasing. Diabetes Canada states that 30% of Canadians are now living with prediabetes or diabetes, and DM2 can reduce life expectancy by up to 10 years.

We know that calling for a change in behaviour is a big ask for our population, but we have to try. We suggest that the approach to accomplish these changes be positive and unifying, concentrating on the message that we can improve our personal health and that of family, friends and neighbours. For example, individual motivation might be enhanced by taking advantage of technologies like continuous glucose monitors, which allows one to see the glucose response to meals.

Herein, we are proposing to help individuals help themselves, starting with something simple, affordable and easily available — achieving personal sufficiency in VitD.

Canadians have Insufficient Vitamin D for Optimal Health.

Evidence has accumulated over decades that our vitamin D (VitD) status is significantly below optimal. For example, Schwalfenberg *et al.* (2010)[2] published a review entitled, "Addressing vitamin D deficiency in Canada: A public health innovation whose time has come." For definitions of deficient and insufficient, they used modest standards: serum VitD levels of less than 25-40 nanomoles/litre (nMol/L) (*i.e.,* 10-16 nanograms/millilitre (ng/mL); 1 nanogram is 1 billionth of a gram) were considered deficient and less than 72-80 nMol/L were considered insufficient. Even employing these standards, they concluded that 70-97% of Canadians were VitD insufficient, and 14-60% were clearly deficient. In the last decade, the field has continued to advance with many clinicians and scientists raising their criteria for sufficiency, making Schwalfenberg's team assessment of Canadians' VitD status look even worse. This was not Schwalfenberg's first attempt to get the attention of the Canadian medical community. He also published a clinical review appearing in the journal Canadian Family Physician in 2007, entitled "Not enough vitamin D — Health consequences for Canadians."[3] If Canada had heeded his advice almost twenty years ago, the health of Canadians and our healthcare system would be far better off today. For now, let us just assume that Canadians and residents of many other northern countries are seriously lacking in VitD. This is supported by Cui *et al*. (2023)[4] in their review entitled, "Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants."

Why is There a Shortage of Vitamin D?

Remember, VitD is called the "sunshine vitamin" for a very good reason: when the cholesterol precursor of VitD, 7-dehydrocholesterol, is exposed to UV-B rays in the skin, VitD3 is created.

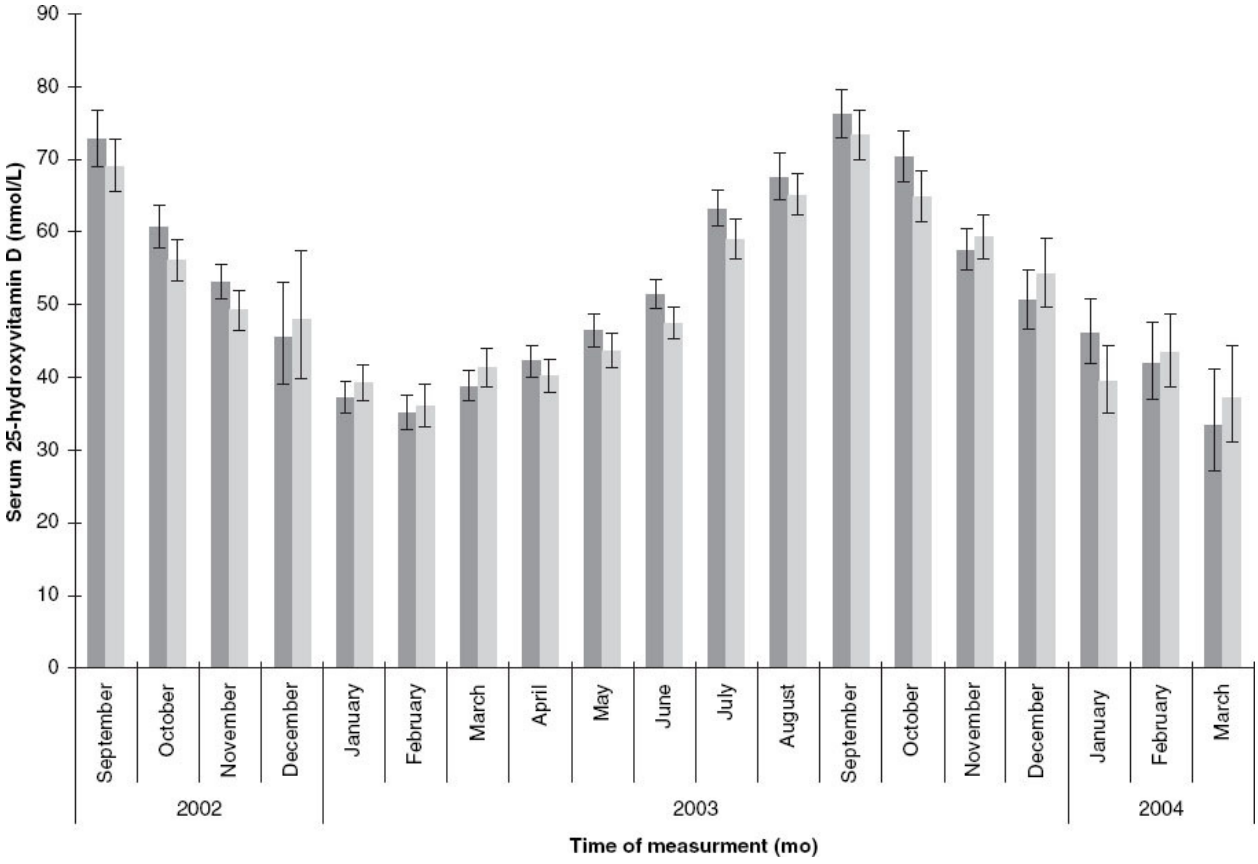
One of the most respected VitD researchers, Michael Holick,[5] explains that "[v]*itamin D made in the skin lasts at least twice as long in the blood as vitamin D ingested from the diet. When you are exposed to sunlight you make not only vitamin D but also at least five and up to ten additional photoproducts that you would never get from dietary sources or from a supplement*."

Seasonal variations in serum VitD for northern countries, such as the United Kingdom, are shown in Figure 1 below.[6] The greater the degree of latitude away from the equator, the lower the level of skin VitD synthesis. Some authors consider latitudes of 37 degrees or more to be of concern. Moreover, time of day is important as more VitD is synthesized when the sun is directly overhead.

There is also evidence that exposure to natural sunlight is important for optimal health, indicating that the red and infrared parts of the spectrum also have important health benefits.

The Vitamin D Society suggests that moderate sun exposure should be considered for those with skin types that do not have a high risk of skin cancer, especially those with darker skin, which tends to make less VitD than light skinned types. The Australian position is now "*people with deeply pigmented skin are at low risk of skin cancer but at high risk of vitamin D deficiency; routine sun protection is not recommended. For those at intermediate risk of skin cancer, sun protection remains a priority, but individuals may obtain sufficient sun exposure to maintain adequate vitamin D status*."[4]

Figure 1. Monthly fluctuation of serum 25-hydroxyvitamin D levels in men (dark grey) and women (light grey) in the United Kingdom. Reproduced from Hyppönen and Power (2007).[6]



Vitamin D Does Much More than Support Bone Health.

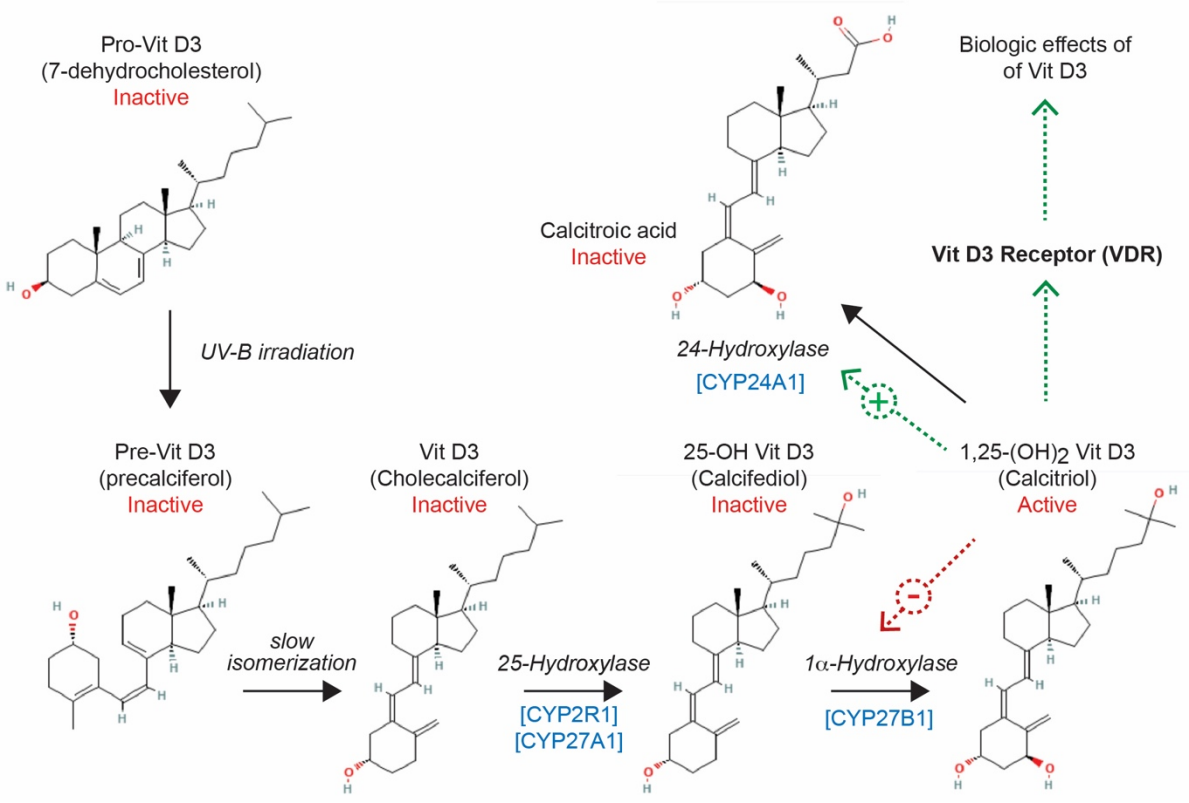
Nowadays, we do not see a lot of weakened and bent bones in our children. Maintenance of bone health was the primary reason for VitD supplementation in products like milk and cereals.

However, it is not quite that simple. While it is true that the weakened and bent bones of Rickets have been documented since the 1600s, now VitD is considered to be of even greater significance as a pro-hormone (or precursor) that has numerous effects throughout the human body. With the work of many different laboratories, we now know that in the skin 7-dehydrocholesterol is made into VitD3 (cholecalciferol), which is then converted to calcifediol (25-OH-VitD3, aka calcidiol) in the liver and then to calcitriol (1,25-$(OH)_2$VitD3) in the kidney. Nevertheless, VitD3 can be converted to calcifediol and calcitriol in other cells/organs for local

activity. These multiple sites may explain the different VitD levels required for different functions, with lower concentrations (50 nMol/L) proving satisfactory for bone health than for immune health (125 nMol/L).

Thus, VitD3 is the hormone precursor, and calcitriol is the active hormone. The circulating levels of calcidiol in blood are used to determine VitD sufficiency. Calcitriol acts through a VitD receptor, VDR (Figure 2). Moreover, Jones (2008) provides the following pharmacokinetic information, "*The lipophilic nature of vitamin D explains its adipose tissue distribution and its slow turnover in the body (half-life approximately 2 mo). Its main transported metabolite, 25-hydroxyvitamin D(3) [25(OH)D(3)], shows a half-life of approximately 15 d and circulates at a concentration of 25-200 nMol/L, whereas the hormone 1alpha,25(OH)(2)D(3) has a half-life of approximately 15 h.*" [8]

Figure 2. Vitamin D metabolism.



This explains why it takes several days to see the therapeutic effects of VitD after it has been ingested.

The concept of the nuclear receptor for VitD3 (VDR) is the next interesting aspect of this story. VDR was discovered in 1969 but subsequently has been found in many cells beyond those involved with calcium metabolism. VDRs are in almost every cell in the human body where they mediate hundreds of different actions, including the direct regulation of over 1000 genes. The VDR is present in cells within all major organ systems — intestine, kidney, cartilage, bone, pancreas, hair follicles, epithelium, endothelium, vascular smooth muscle, cardiomyocytes, and immune cells such as leukocytes. When calcitriol enters a cell, it binds to the VDR, which then starts a chain reaction of events activating some genes and suppressing others. Some examples of genes that are activated are those for immune-related genes such as *CD14*, and *NOD2*, which are the first receptors to recognize invading pathogens. Genes for cathelicidin and β2 defensin, peptides with antimicrobial and antiviral activity, are also activated. Examples of suppressed genes include those for interferon-gamma, which drives cellular immunity, and hepcidin, a master regulator of iron homeostasis.

What is the Scope of Vitamin D3 Effects?

There are VDRs almost everywhere in the human body, indicating the wide breadth of VitD functions. In the face of VitD insufficiency, there will be suboptimal health seen as exacerbations of diseases of various organs/tissues. As already mentioned, Rickets (lack of bone health) is well known, but there are many other indicators of suboptimal health as described in the reviews by Grober *et al*. (2013)[9] and Maretzke *et al.* (2020).[10] For the purposes of this proposal, we suggest considering diseases that affect major portions of Canadian society, using statistics for the leading causes of death as a guide.

Leading causes of death in Canada in 2021[11]

- Cancers – 26.6%
- Heart disease – 17.7%
- Accidents – 6.2%
- COVID-19 – 4.6%
- Stroke – 4.3%
- Chronic lower respiratory diseases – 3.5%
- Diabetes – 2.4%

Of these seven categories, only accidents stand out as being unrelated to inadequate VitD. **Appendix I** provides more detail on each target condition.

Should We Supplement the Population with Vitamin D?

By supplementing with VitD, we anticipate significant reductions in the healthcare load attributed to the other 6 leading conditions. A study published in 2021 for the UK, which has similar VitD challenges as Canada, revealed that "*increasing levels in serum 25(OH)D were independently associated with a decreased risk of all-cause and cause-specific mortality*."[12] The measurement of serum 25(OH)VitD is the usual manner of estimating VitD status.

To provide optimal health for Canadians, an important step is ensuring VitD sufficiency for all the functions listed above. This means raising the bar above the amount required for bone health. The evidence currently available for immune health indicates a serum VitD target of 125-150 nMol/L, which is usually attained with a daily dose of 3000-5000 IU, compared with the dose suggested for bone health of 600-800 IU/day (Health Canada). While precise target values for other potential beneficial effects of VitD sufficiency are desirable, there is now sufficient information to allow us to act now. The benefit-to-risk ratio for infections alone is sufficient to support ensuring sufficiency of VitD in the population, especially since the toxicity levels of VitD are much less of a concern than previously thought. Toxicity concerns will be discussed below.

Caveats.

Not all people will benefit from VitD supplementation because some are already VitD sufficient and do not require additional doses of this nutrient. This accounts for why some participants in clinical studies do not show a health benefit from VitD supplementation. Nevertheless, by corollary, those who are most deficient are likely to benefit most. Also, some people will be genetically predisposed to having low VitD levels despite supplementation, while others may have comorbidities affecting liver or kidney function; for these individuals, a different form of VitD may be required to attain adequate levels of bioactive calcitriol.

In several studies, especially when a rapid response was sought, VitD treatment was found to be ineffective; we suggest that the active form, calcitriol, should have been given. Accordingly, Entrenas Castillo *et al.* (2020) observed less morbidity and mortality when they treated a viral illness (COVID-19) with calcidiol, a hydroxylated metabolite of VitD3.[13]

Requirements for Vitamin D3.

Because VitD3 is made by exposure to sunlight, we are most sufficient during the summer. But there are many other variables that determine the levels of circulating VitD. These include the area of skin exposed, skin colour, duration of exposure, use of sun block and more. VitD is also available following consumption of especially fatty fish and fish oils, red meat, egg yolk, mushrooms, and fortified products such as cereals, cow and plant-based milks. For these reasons, it is a priority to invest in lab testing for individual serum VitD levels (tested as calcidiol). Mid-summer and mid-winter may be appropriate times to determine maximum and minimum levels, respectively. Note that VitD is fat soluble, and if supplements are used, these should be taken with food containing lipids to improve absorption.

The cost of VitD testing ranges from $32 to $93 across Canada. With some ingenuity and efficiencies of scale, the cost-savings should be considerable — perhaps in the range of less than $10/test.

Dose of Vitamin D.

McCullough *et al.* (2019)[14] studied more than 4,700 patients in a psychiatric hospital who agreed to VitD supplementation with either 5,000 or 10,000 IU/day. Some took larger doses ranging from 20,000 to 50,000 IU/day. They found that "*there have been no cases of vitamin D3 induced hypercalcemia or any adverse events attributable to vitamin D3 supplementation in any patient*." Hypercalcemia is excess calcium in the blood that can result in bone pain, muscle weakness, stomach upset, nausea, vomiting and constipation. Controls (777 non-supplemented subjects) had mean calcidiol/25-OH-VitD3 levels of 27.1 nanograms/milliliter (ng/mL) (range 4.9 to 74.8 ng/mL; supplemented subjects (418) had calcidiol/25-OH-VitD3 levels of 118.9 ng/mL (range 74.4 to 384.8 ng/mL). Unsupplemented subjects produced mean serum calcium 0.95 mg/ml; supplemented subjects showed a mean of 0.96 mg/mL. Ranges did not vary significantly, as

unsupplemented subjects had a range of 0.84 to 1.07 mg/mL, whereas supplemented subjects fell within a range of 0.86 to 1.07 mg/mL. Thus, supplementation with VitD3 doses of 5,000 to 50,000 IU/day for 12 to 29 days appeared to have been safe. There have been other studies published with similar results and conclusions.

Historically, doses of 60,000 to 300,000 IU/d have been used for asthma, 150,000 to 600,000 IU/d for rheumatoid arthritis, and 100,000 to 150,000 IU/d for tuberculosis infections.[14] A comprehensive review by Vieth (2007)[15] on the risk of daily dosing with VitD also concluded that 10,000 IU/day should be the safe tolerable upper intake level, and estimated that calcidiol/25OHD3 blood levels above 240 ng/mL were required to result in clinically significant hypercalcemia.

For context, the VitD made by human skin can be in the order of 20,000 IU in less than a day, as reported in a 2019 publication by Religi *et al*.[16] based on data from Switzerland, a country at similar latitude to Canada. These authors found that in summer and spring, with 22% of skin exposed to sunlight, 1,000 IU vitamin D doses are synthesized in 10-15 minutes of sun exposure for adults, or about 4,000-6,000 IU/h. A longer day in the sun is often said to result in a dose of VitD of 20,000 to 25,000 IU.

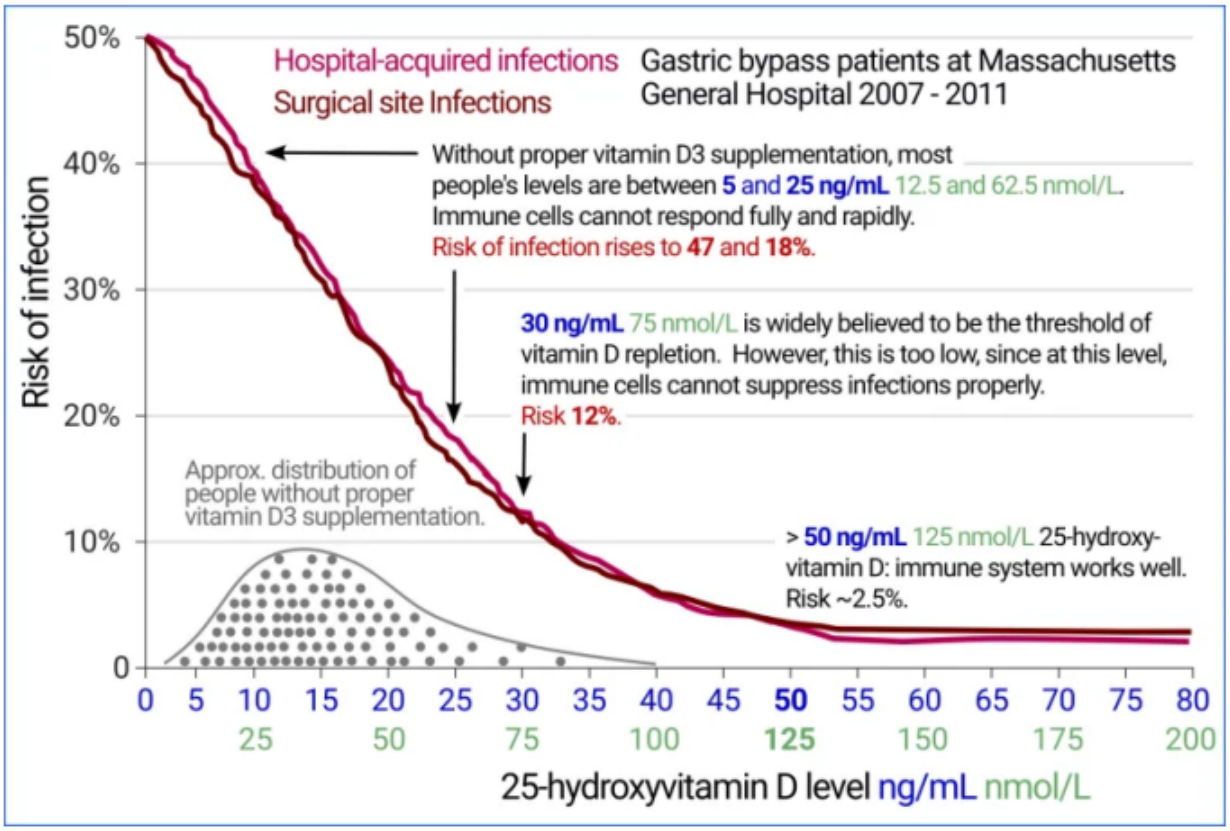
Appendix 1 comprises references that describe doses of VitD that have been suggested to address the various hypovitaminosis D conditions (low levels of VitD). The range is from 4,000 to 10,000 IU/day. The published information indicates that a daily dose of 4,000-6,000 IU should be safe for the population and satisfy most requirements for optimal health.

Unfortunately, Health Canada based its guidelines on an error of calculation found in the 2011 Institute of Medicine report. In a peer-reviewed paper of Veugelers and Ekwaru[17], this figure was corrected, and they stipulated the amount of VitD required to be over 8000 IU/day. They state that, "*8895 IU of vitamin D per day may be needed to accomplish that 97.5% of individuals achieve serum 25(OH)D values of 50 nMol/L or more*." Now that the error has been corrected, it would be logical for Health Canada to amend their current recommendation of 400-800 IU/day.

In summary, we cannot recommend dosing for individuals because there is considerable inter-individual variability in the dose-to-blood level relationship, for the reasons described above. We

favour checking individual VitD levels to guide personal dosing. The reference range used by Life Labs, Ontario's provider of laboratory services, is 75-250 nMol/L. Based on the graph provided below, we suggest assessment in February and September for minimum and maximum serum levels, and patients in consultation (with their family doctors) might consider a serum VitD level of 125 nMol/L to be the desired target.

Figure 3. Target serum level. Graph from Quraishi *et al*. (2014).[18]



Health care savings.

Considering the breadth of VitD actions and its necessity for health, hypovitaminosis D must be a substantial drain on Canadian healthcare. Grant *et al.* (2010)[19] have estimated the cost of VitD insufficiency for the country. Using both international and Canadian databases, these authors have estimated the cost of insufficient VitD contributing to morbidity rates in cancer, cardiovascular disease, type 2 diabetes, multiple sclerosis, falls/fractures, influenza/pneumonia,

septicemia and complications of pregnancy. Total health spending in Canada was estimated to be $344 billion in 2023.[20] And the proportion of this due to VitD being 67 nMol/L instead of 100 nMol/L was conservatively estimated to be 6.9%; in other words, if Canada's population were to raise their VitD levels to the recommended levels, the annual savings would be about $23.7 billion.

But it would do more than just save money; it would significantly reduce the strain on healthcare facilities and personnel (doctors, nurses, pharmacists, technologists, *etc*.). However, the most important advantage would be an improvement in the health of all Canadians, even for those having difficulty accessing primary care.

Implementation.

We appreciate that overcoming hypovitaminosis D in more than 40 million people will be a challenge. But we know it is possible — after all, we vaccinated over 30 million citizens in a few months during 2021 — even if it cannot be implemented immediately (but sooner is better). A project like this needs thorough, ongoing evaluation. Fortunately, ample data may be collected and analysed alongside the implementation of the VitD testing and supplementation project for very little additional cost.

We suggest that this should be considered as a research project conducted under the auspices of Canada's three federal research agencies: the Canadian Institutes of Health Research, the National Science and Engineering Research Council, and the Social Sciences and Humanities Research Council. Involving these bodies has the potential to attract experienced investigators, competent administrators and enthusiastic graduate students to continue to research VitD. But considering funding at this point is putting the cart before the horse; let us first agree on the benefits of widespread supplementation, and then decide how best to implement the plan.

Vitamin D toxicity.

VitD is fat-soluble, raising a concern that like other similar substances, it could accumulate in the human body to induce a toxic reaction. Despite this possibility, the occurrence of adverse reactions among those taking VitD supplements has been remarkably rare. Because regular body

exposure to direct sunlight can create as much as 20,000 IU in half an hour, perhaps excellent tolerance of VitD supplements could have been anticipated. Nevertheless, several reports of VitD toxicity have been reported in the literature. The fact that case reports worthy of publication suggests that the risk of VitD intoxication is rare but real. As described by Alkundi *et al.* (2022)[21] in their case report, a middle-aged male had taken 15,000 IU daily for four months. He complained of recurrent vomiting, nausea, abdominal pain, leg cramps, tinnitus, dry mouth, increased thirst, diarrhoea, and weight loss. His blood tests revealed elevated serum calcium, creatinine and urea. His serum VitD was recorded as above 400 nMol/L, which, though high was below the toxicity level of 750 nMol/L subscribed to by some investigators. The 250 nMol/L recommended by the present authors should ensure a good safety margin.

Holick (2015)[22] in an editorial entitled "Vitamin D Is Not as Toxic as Was Once Thought: A Historical and an Up-to-Date Perspective" stated, "*Vitamin D intoxication associated with hypercalcemia, hyperphosphatemia, and suppressed parathyroid hormone level is typically seen in patients who are receiving massive doses of vitamin D in the range of 50,000 to 1 million IU/d for several months to years. Ekwaru et al.[23] recently reported on more than 17,000 healthy adult volunteers participating in a preventative health program and taking varying doses of vitamin D up to 20,000 IU/d. These patients did not demonstrate any toxicity, and the blood level of 25(OH)D in those taking even 20,000 IU/d was less than 100 ng/mL. For point of reference, a 25(OH)D level of 100 ng/mL is considered by the Institute of Medicine, the Endocrine Society, and many reference laboratories to be the upper limit of normal*."

The number of cases of VitD toxicity as reported in VigiAccess (World Health Organization database of adverse drug reactions) has varied from a high of 1,136 cases in 2019 to a low of 781 cases in 2022. This compares favourably with acetaminophen (aka paracetamol or Tylenol) which had 22,734 adverse effect cases reported in 2019 and 12,329 cases in 2022.

According to Holick (2022) [24] lifeguards typically have reported levels of calcidiol/25-OH-VitD3 of 100-125 ng/mL and there are no cases of VitD intoxication from sun exposure. VitD intoxication was defined as a 25-OH-VitD3 greater than 150 ng/mL (375 nMol/L) associated with hypercalcemia, hypercalciuria and often hyperphosphatemia. Similarly, Hathcock *et al.* (2007)[25]

have concluded that the absence of toxicity in trials conducted in healthy adults indicates the VitD dose ≥0.25 mg or 10,000 IU/day can be considered a safe upper limit.

One means by which the body defends itself against VitD toxicity is through induction of the cytochrome P450 enzyme CYP24A1 by calcitriol/1,25(OH)$_2$VitD3. This prevents the accumulation of toxic levels of calcitriol/1,25(OH)$_2$VitD3 and calcidiol/25-OH-VitD3 by catalyzing the formation of an inactive metabolite, calcitroic acid (as shown in Figure 2).

VitD Toxicity in Pets.

Users may know that VitD in large doses has been developed as an alternative to warfarin as a vermin (rat) poison. Nevertheless, for pets such as dogs and cats to become intoxicated, they would have to ingest much more VitD than the doses normally taken by humans. The main risk for pets would be ingestion of VitD containing rodenticide baits.[26] The oral lethal dose for 50% death (LD_{50}) of cholecalciferol in rats is 43.6 mg/kg (1,744,000 IU/kg).

Vitamin K2 to The Rescue?

We now know that vitamin K2 has many important beneficial effects, one of which is to ensure proper distribution of calcium into bones and away from soft tissues, especially blood vessels. This would address some of the effects of hypercalcemia resulting from excess VitD. As this document is focused on VitD, we refer the reader to a useful recent review by Kozioł-Kozakowska and Maresz (2022)[27] on vitamin K2 in children's health and diseases.

A first principle in the nutrition field is that proper or optimal nutrition is the result of all of the individual components working and acting together. Thus, VitD works best when combined with optimal supplies of several other nutrients such as vitamin K2. We do not have to wait for expensive, controlled trials to act in the best interests of our citizens. As we have demonstrated, there is already enough evidence to justify VitD supplementation. Individual citizens, working with their doctors and other healthcare professionals, can take existing information on VitD *per se* and combine it with knowledge of vitamin K2 to further optimize their health maintenance. While it is known that magnesium is also important in the context of VitD sufficiency, this subject

is reserved for another article. These and similar refinements can be pursued in the wider implementation of a national strategy on nutritional optimization for health maintenance.

Confounding factors.

A major difference between studies on VitD and other treatments, such as novel drugs, is the impossibility of comparing a group with VitD against a group without VitD. There can be no such control population because everyone has some level of VitD in their bodies.

Vitamin D Testing.

The rationale presented above is intended to ensure that VitD is used effectively and safely. A key factor in implementing VitD sufficiency for all citizens would be the opportunity to access VitD testing. Currently, this test is not covered by all provincial health plans, but it is still covered in Quebec.

Nevertheless, we have established that such testing would be a health investment that would pay for itself many times over. Moreover, with a national VitD initiative, market forces almost certainly could drive the introduction of cheaper and more convenient tests to measure VitD levels.

Appendix 1- Benefits of Vitamin D Supplementation.

The literature on VitD is massive and cannot be covered comprehensively in this document. Nonetheless, it is possible to cite sufficient examples of studies and reviews to illustrate the potential benefits of full VitD sufficiency of the Canadian population.

- **All-cause mortality**.

  In a study by Dai *et al.* (2021),[28] the authors noted that, "*among 37,079 patients with CVD at baseline, 57.5% were subjected to [sic] vitamin D deficiency (i.e., 25[OH]D <50 nMol/L). During a median follow-up of 11.7 years, 6,319 total deaths occurred, including 2,161 deaths from CVD, 2,230 deaths from cancer, 623 deaths from respiratory disease, and 1,305 other-cause deaths. We observed non-linear inverse associations for all-cause, cancer, respiratory disease, and other-cause mortality (P-non-linearity <0.01) and approximately linear inverse associations for CVD mortality (P-non-linearity = 0.074). Among CVD patients with vitamin D deficiency, per 10 nMol/L increment in serum 25(OH)D concentrations was associated with an 12% reduced risk for all-cause mortality and 9% reduced risk for CVD mortality*."

- **Multiple sclerosis (MS).**

  With respect to VitD application, this is a good news story as MS specialists recommend VitD supplementation.

  MS, a disease affecting the brain/spinal cord to produce significant disability, features an incidence that increases with increasing latitudes. Consequently, populations (like that of Canada) further from the equator have more MS cases.[29] This led to the concept that insufficient VitD is a factor in the development of MS. Also, genetic studies in MS have unveiled abnormalities of VitD metabolism linked to an increased risk of MS.[30] For information regarding the mechanism of VitD effects in MS, see immune effects below. Several studies have addressed the potential utility of VitD for the prophylaxis and treatment of MS.[31] Nevertheless, robust clinical trials unequivocally revealing the benefit of VitD in this disease are still lacking, primarily due to lack of sufficient funding. On the basis of current evidence,

MS specialists and the MS Society of Canada recommend supplementation with VitD[32,33] (Table 1). They stated that "*adults should achieve and maintain a normal vitamin D status with monitoring by physicians (serum 25-hydroxyvitamin D (25OHD) = 50–125 nmol/L, requiring intake of 600–4000 IU vitamin D/day).*" Also, "*Because low serum 25OHD during childhood and adolescence is associated with increased MS risk, pregnant women, newborn infants, and all youth should follow DRI (Dietary Reference Intake) recommendations for vitamin D intake, including age specific recommendations for vitamin D supplements*."

Table 1. Recommended daily intake of VitD. Table 1 is reproduced from the document "MS Society of Canada Recommendations on Vitamin D in MS."[33] These guidelines also state that "*people living with MS should target serum 25-hydroxyvitamin D of 50–125 nmol/L.*"

Age group	**Recommended daily intake**	**Maximum daily intake**
Infants 0-6 month-olds	400 IU	1000 IU
Infants 7-12 month-olds	400 IU	1500 IU
Children 1-3 year-olds	600 IU	2500 IU
Children 4-8 year-olds	600 IU	3000 IU
Children and adults 9-70 year-olds	600 IU	4000 IU
Adults >70 year-olds	800 IU	4000 IU
Pregnant and breastfeeding women	600 IU	4000 IU

- **Cancers.**

Two factors work against researchers attempting to demonstrate that VitD decreases the incidence of cancers: the long period between exposure to a carcinogen and diagnosis of cancer; and the variability in blood levels of VitD, especially in lower latitudes where greater exposure to sunlight is possible. The duration effect as portrayed in the second figure from a study by Chandler *et al.* (2020),[34] indicates that the cumulative incidence of metastatic and fatal cancers of any type show no effect of VitD supplementation for two years, but then show greater protective effects of VitD in subsequent years.

Wu *et al*. (2023)[35] in their recent prospective study of data from the UK Biobank comprising 97,621 participants revealed that individuals with metabolic syndrome but with sufficient VitD status (> 75 nMol/L) had a 25% and 35% lower risk for 16 different cancers and all-cause

mortality, respectively, over 12.7 years as compared to those with VitD deficiency (< 25 nMol/L).

Song *et al.* (2018)[36] conducted a meta-analysis on the effects of VitD on mortality in patients with prostate cancer. Seven eligible cohort studies with 7,808 participants were included. Higher VitD levels correlated with decreased mortality from prostate cancer as each 20 nMol/L increment in calcidiol/25-OH-VitD3 level was associated with a 9% lower risk of all-cause mortality and prostate cancer-specific mortality.

- **Cardiovascular diseases (CVD).**

Although there are many reviews indicating that adequate VitD is associated with reduced cardiovascular diseases, there is still much research needed to define the extent of the clinical response and the exact mechanisms involved. Nevertheless, the extant evidence is arguably sufficient to recommend VitD supplementation as part of the strategy to prevent and treat many cardiovascular diseases. In other words, we suggest that VitD supplementation applied to the VitD insufficient population is justified now, and that further delay is tantamount to causing harm.

The risk of cardiovascular disease with respect to VitD levels was analyzed by Zhou *et al.* (2022)[37] examining data from the UK Biobank with 44,519 CVD cases and 251,269 controls. They estimated the potential reduction in CVD incidence attributable to a correction of low VitD status. There was an L-shaped association between genetically predicted serum 25-OH-VitD3 and CVD risk (P non-linear = 0.007), where CVD risk initially decreased steeply with increasing concentrations and levelled off at around 50 nMol/L. A similar association was seen for systolic (P non-linear = 0.03) and diastolic (P non-linear = 0.07) blood pressure. Bringing serum 25-OH-VitD3 levels above 50 nMol/L was predicted to result in a 4.4% reduction in CVD incidence (95% confidence interval: 1.8– 7.3%). They concluded that VitD deficiency can increase the risk of CVD and that CVD could be reduced by population-wide correction of low VitD status.

With respect to hypertension, there are strong data indicating that VitD deficiency likely plays an important role in the development of this condition. Moreover, a plausible mechanism has been revealed using laboratory animal studies. The Ludwigshafen Risk and Cardiovascular Health (LURIC) study[38] showed that 1,25$(OH)_2$VitD3 was inversely associated with levels of hypertensive factors, plasma renin and angiotensin II. VitD analogues suppress plasma renin activity in patients. The mechanism as elucidated in animals is that 1,25$(OH)_2$VitD3 inhibits renin gene transcription through the cyclic-AMP signalling pathway.[39]

- **Lung diseases. Bacterial and viral pneumonia.**

A systematic review and meta-analysis by Martineau *et al.* (2017)[40] comprising 11,321 participants from 25 eligible randomized placebo-controlled trials having individual participant data, provided high quality evidence to support that VitD supplementation is a safe intervention to prevent the risk of acute respiratory tract infections. In another review, Borshe *et al.* (2021)[41] addressed the question of whether poor VitD status is caused by respiratory illness, or whether VitD deficiency predisposes an individual to SARS-CoV-2 infection and severe COVID-19 disease. Accordingly, they included studies in which patients' pre-infection VitD levels were documented and also some in which VitD levels up to the day after hospitalization were recorded. Their analysis revealed a significant negative correlation between VitD pre-infection concentrations and mortality. Extrapolation of the regression line to the *x*-axis implied that the risk of death could virtually disappear at 125 nMol/L, representing the therapeutic target for circulating calcifediol/25-OH-VitD3 needed for optimal immune function. Indeed, recent studies have demonstrated that the VitD status of hospitalized COVID-19 patients was inversely associated with chest X-ray severity scores and various biomarkers of inflammation and clotting activity, including tumour necrosis factor-alpha, interleukin-6, C-reactive protein, ferritin and D-dimer levels.

- **Brain diseases (Alzheimer & Parkinson).**

In a recent review, Pinzon *et al*. (2023)[42] included a total of 6 studies, involving 10,884 participants. The analysis showed that patients with VitD deficiency (< 25 ng/mL) had a higher

risk of Alzheimer disease compared to patients with adequate VitD (≥ 25 ng/mL) (HR: 1.59, 95% CI: 1.09, 2.33, I2=77%).

A subsequent study by Ghahremani *et al.* (2023)[43] reported that VitD exposure was associated with 40% lower dementia incidence versus no added VitD exposure. The University of Calgary team "*prospectively explored associations between vitamin D supplementation and incident dementia in 12,388 dementia-free persons*" using data from the National Alzheimer's Coordinating Center database. There were 12,388 participants in the VitD supplemented group, who had been exposed to some form of VitD supplements, and 4,637 controls who had not taken any VitD supplements. From all subjects, 2,696 progressed to dementia in 10 years; of these 2,017 (74.8%) had no VitD supplements and 679 (25.2%) were exposed to VitD supplements. After several adjustments, VitD exposure was associated with a 40% lower incidence of dementia (HR=0.60, 95% CI: 0.55–0.65, p<0.001). Remarkably, this benefit of VitD supplementation was observed despite the lack of any attempt to optimize the dose of VitD consumed. It is tempting to suggest that VitD supplementation could lower the odds of dementia by more than 40%.

Considering Canada's aging population and increasing diagnoses of dementia, widespread VitD supplementation would appear to be a logical beneficial public health measure.

- **Type 2 diabetes (DM2).**

A review by Pittas *et al.* (2013)[44] of three randomized trials revealed that in adults with prediabetes, VitD was effective in decreasing the risk for diabetes. Among participants assigned to the VitD group, who maintained an intra-trial mean serum 25-OH-VitD3 level of at least 125 nMol/L (≥50 ng/mL) compared with 50 to 74 nMol/L (20 to 29 ng/mL) during follow-up, cholecalciferol/VitD3 reduced the risk for diabetes by 76% (hazard ratio, 0.24 [CI, 0.16 to 0.36]), with a 3-year absolute risk reduction of 18.1% (CI, 11.7% to 24.6%).

- **Inflammatory bowel disease (Crohn's disease, ulcerative colitis).**

  The impact of sunlight exposure upon the severity of Crohn's disease has been observed as determined by the correlation between a necessity for surgery and less opportunity to receive UV light. Accordingly, Govani *et al*. (2014)[45] observed that CD patients living in zones in the upper tertile of UV sunlight had the least CD severity and those in the lower tertile had the greatest severity.

  In 201 CD patients in Saskatoon, Saskatchewan, Alrefai *et al*. (2017)[46] documented an inverse association between VitD status and objective indicators of disease activity. The authors used these criteria: < 30 nMol/L to define VitD deficient, 30–50 nMol/L for insufficient, 51–74 nMol/L for adequate, and > 75 nMol/L for optimal. VitD deficiency was significantly associated with elevated C-reactive protein scores compared with the three groups characterized by better VitD status. We recommend that CD patients be assessed regularly for VitD, and supplementation provided accordingly as proposed by Wimalawansa (2023).[47]

  Similarly, the association of VitD deficiency and inflammatory bowel disease (IB) in young people has been reviewed by Fatahi *et al*. (2023).[48]

  In a small (n=40) double-blind, placebo controlled trial, Bendix *et al*. (2021)[49] determined that high dose VitD treatment for seven weeks had a beneficial effect. They noted that treatment with a 5 mg or 200,000 IU bolus followed by 0.5 mg or 20,000 IU/day for 7 weeks reduced the need for more infliximab treatment and reduced inflammatory markers.

  In an English abstract of a French paper, Berriche-Yahi *et al*. (2022)[50] reported on 262 VitD deficient (< 50 nMol/L) CD patients who were treated with VitD, either 200,000 IU/month or 6,000 IU/day. Both groups responded with serum 25-OH-D3 improving to normal after 6 and 12 months. Clinically "*vitamin D supplementation allowed the clinical remission phase*." More specifically, treatment with daily VitD was superior to monthly larger doses. They suggested that VitD supplementation could "*extend the remission phase and to avoid the surgical bowel resection*."

Similarly, Jorgenson *et al*. (2010) [51] reported that 1200 IU VitD/day for 12 months decreased the relapse rate in CD from 29% to 13%, (P=0.06).

- **Immune system.**

Leukocytes such as activated B and T lymphocytes, macrophages, dendritic cells, neutrophils, mast cells and eosinophils express VDR,[52,53] as well as the enzymes CYP27B1 and CYP24A1, which enable leukocytes to regulate intracellular bioactive VitD levels. Collectively, these support an important immunomodulatory role for VitD. This explains why VitD deficiency has been found to be a risk factor for microbial infection, especially intracellular bacterial and viral diseases, immune disorders including autoimmune diseases and allergies and cancers.[54]

Numerous genes involved in immunoregulation are directly responsive to VDR after it has bound to VDR response elements within gene promoter or enhancer regions;[55] examples include genes regulating antigen presentation (MHC genes), cell trafficking (chemokines and chemotactic agents), cell activation (cytokines), pathogen recognition (pattern-recognition receptors) and antimicrobial peptides.[56] However, VitD also has non-genomic mechanisms of regulating immediate leukocyte function that include binding to an alternate VDR (PDIA3) found within the cell membrane, cytoplasm, mitochondria and nucleus.[57]

VitD's immunomodulatory properties are broadly attributed to regulating leukocyte differentiation, maturation, responsiveness to cytokines and chemokines, and cell metabolism.[58] More specifically, VitD regulates cells of the innate immune system by supporting production of neutrophil antimicrobial peptides, differentiation of inflammatory M1 macrophages to tissue repairing M2 macrophages and arresting dendritic cell maturation so that they remain capable of producing immunological tolerance. In terms of the acquired immune system, VitD supports the terminal differentiation of T cells to regulatory T cells instead of inflammatory Th1 and Th17 cells, and apoptosis (programmed cell death) of activated B cells. It also inhibits B cell differentiation into immunoglobulin-producing plasma cells and their consequent immunoglobulin class switching.

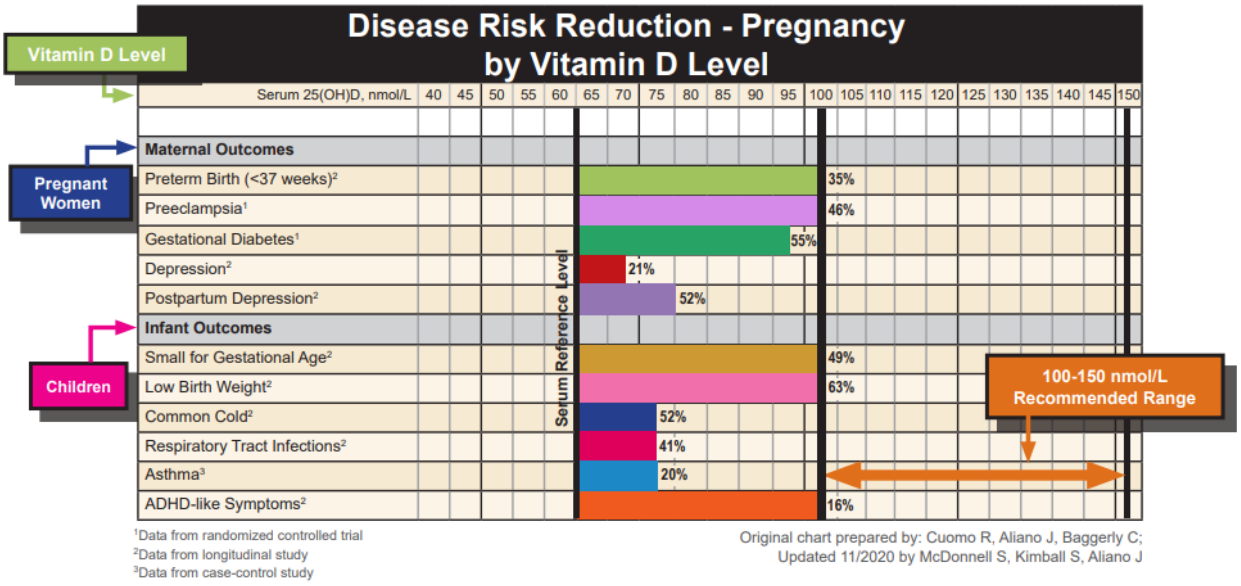
Schwalfenberg (2010)[59] has suggested that the several infectious conditions such as tuberculosis, chest infections, wound infections, influenza, urinary tract infections, eye infections and wound healing may benefit from adequate VitD.

- **Pregnancy and vitamin D.**

The concepts of Developmental Origins of Health and Disease (DOHaD aka fetal programming) describe how maternal nutrition during pregnancy affects the health of offspring during later life, including adulthood. Exactly how VitD might play a role in DOHaD is yet to be elucidated. Nevertheless, Amegah *et al.* (2017)[60] have found that VitD insufficiency was associated with risk of preterm birth. In their report entitled "Vitamin D: Before, during and after Pregnancy: Effect on Neonates and Children", Mansur *et al.* (2022)[62] described evidence that VitD is helpful in reducing the risk to mothers of pre-eclampsia, gestational diabetes, caesarean section and preterm delivery as well as reducing the risk to their offspring of low birth weight, low bone mass and possibly also bronchiolitis, asthma, type 1 diabetes, multiple sclerosis and autism. Further, VitD deficiency during gestation appears to result in increased risk of obesity in offspring.[63]

Supplementation of mothers with VitD during pregnancy affects the microbial population of their progeny,[64] which may have positive implications for asthma and respiratory infections.

Much of this is presented graphically in the chart below[65], showing the beneficial effects of VitD elevation in pregnant women for both mother and child.



- **Mental health**.

Although studies on the relationship between VitD and mental health are sparse compared with those on physical health, most such reports indicate that adequate VitD is necessary for good mental health. At the earliest stage of life, optimal maternal VitD appears to be essential for the good mental health of offspring.[65] Thus, low maternal VitD dosage during gestation has been related to a significantly greater risk of developing schizophrenia and other severe mental illnesses in later life.

During childhood, VitD is similarly necessary for good mental health. In their article "The Influence of Vitamin D Intake and Status on Mental Health in Children: A Systematic Review," Glabska *et al.* (2021)[66] addressed "*behavior problems, violence behaviors, anxiety, depressive symptoms/depression, aggressive disorder, psychotic features, bipolar disorder, obsessive compulsive disorder, suicidal incident, as well as general patterns, as follows: mental health, level of distress, quality of life, well-being, mood, sleep patterns*." Included were both interventional and observational studies. With few exceptions, the data indicated a positive relationship between supplementary treatment with VitD and mental health, and between VitD levels and mental health indicators. This relationship was apparent even though the doses of VitD used in such studies was generally in a range that would be considered moderate

compared to the higher doses being used in contemporary physical medicine, and the VitD blood level criteria were also moderate.

Guzak *et al.*'s (2021)[67] literature review of the effect of VitD supplementation on mental health in healthy adults shows a marked difference between studies of adults and studies of children. These authors found that "*results of the majority of studies did not confirm a positive influence of vitamin D supplementation*." The authors also commented on the difficult confound encountered when evaluating the effect of VitD treatment, as there is always a background level of VitD. This varies significantly based on cultural variables such as diet and location. Accordingly, we cannot suggest a standard VitD intake or blood level for the maintenance of optimal mental health in adults.

- **Oral health.**

VitD deficiency has a significant effect on oral health. This should not be surprising considering the role that VitD plays in the mineralization of teeth and their supporting alveolar bone. In addition, this vitamin assists in maintaining the integrity of the gums and, via saliva, assists in modulating immunologic and antimicrobial activities.

VitD deficiency results in defective dentition in which the enamel is thinner or less mineralized than normal, and the dentine or inner hard layer is less mineralized. The pulp chamber containing blood vessels and nerve fibres is larger than normal and tooth roots are shorter than usual.[68] These physical defects are associated with teeth that are prone to fracture, malocclusion, and periodontal disease.[69] While current evidence indicates an association between VitD deficiency and increased dental decay in children and adults, the mechanisms underlying this association remain unclear.[70]

Faulty development of the enamel can occur *in utero*. Classically this appears as a band of poorly formed or pitted enamel on the deciduous teeth corresponding to the period at which the mother was subject to a VitD deficiency. Supplementation with VitD during pregnancy has been associated with a 50% reduction in enamel defects of the newborn.[71]

Periodontitis is a polymicrobial chronic inflammatory disease that destroys the soft and hard tissues supporting the tooth in its socket, resulting in increased tooth mobility and possible tooth loss. Although VitD deficiency might affect tooth mineralization and that of the supporting alveolar bone, thus promoting periodontitis, the relationship between Vitamin D levels and periodontitis remains uncertain.[72] Several studies have demonstrated an association between decreased levels of VitD and the clinical signs of periodontitis, such as inflamed, bleeding gums.[73,74]

There are reports that pregnant women with lower levels of serum VitD have moderate to severe periodontitis compared to women with good periodontal health.[75] The non-surgical treatment of periodontitis has benefitted from VitD and calcium supplementation, again supporting a relationship between adequate levels of VitD and periodontal integrity.[76] Orthodontic treatment depends on alveolar bone resorption in front of the moving tooth and bone formation behind it. Animal studies have demonstrated that by interfering with bone metabolism, VitD deficiency inhibits tooth movement and induces treatment complications. Further research might indicate the usefulness of VitD supplementation in minimizing the complications and reducing the duration of orthodontic therapy.[77] VitD deficiency has been associated with an increased risk of oral, esophageal, and pharyngeal cancers.[78] Foci of osteonecrosis (dead bone) within the mandible or maxilla occasionally occur following radiation therapy for oral and pharyngeal malignancies and as a side effect of bisphosphonate (Fosamax) therapy in controlling osteoporosis. It is yet undetermined as to whether VitD deficiency is a risk factor for the development of osteonecrosis or if VitD supplementation will reduce its occurrence.[79]

VitD deficiency reduces the flow rate of saliva and its ability to neutralize the acidogenic bacteria responsible for dental decay.[80] These factors, in combination with a loss of salivary immune regulation and antimicrobial properties, may explain the association between VitD deficiency and increased susceptibility to dental decay and the promotion of oral pathogens.[81]

Of the total estimated Canadian health expenditure for 2022 of $344 billion,[82] 5% or $1.5 billion can be attributed to oral diseases, most commonly tooth decay and periodontitis. The

association between these conditions and VitD deficiency justifies maintaining optimal levels of VitD.

References.

1. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001 Sep 13;345(11):790-7. doi:10.1056/NEJMoa010492. https://pubmed.ncbi.nlm.nih.gov/11556298/
2. Schwalfenberg GK, Genuis SJ, Hiltz MN. Addressing vitamin D deficiency in Canada: a public health innovation whose time has come. Public Health. 2010 Jun;124(6):350-9. doi:10.1016/j.puhe.2010.03.003. https://pubmed.ncbi.nlm.nih.gov/20413135/
3. Schwalfenberg G. Not enough vitamin D: health consequences for Canadians. Can Fam Physician. 2007 May;53(5):841-54. https://pubmed.ncbi.nlm.nih.gov/17872747/
4. Cui A, Zhang T, Xiao P, Fan Z, Wang H, Zhuang Y. Global and regional prevalence of vitamin D deficiency in population-based studies from 2000 to 2022: A pooled analysis of 7.9 million participants. Front Nutr. 2023 Mar 17;10:1070808. doi:10.3389/fnut.2023.1070808. https://pubmed.ncbi.nlm.nih.gov/37006940/
5. Holick, MF. (2010) The Vitamin D Solution, Hudson Street Press: 158.
6. Hyppönen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007 Mar;85(3):860-8. doi:10.1093/ajcn/85.3.860. https://pubmed.ncbi.nlm.nih.gov/17344510/
7. Neale RE, Beedle V, Ebeling PR, Elliott T, Francis D, *et al*. Balancing the risks and benefits of sun exposure: A revised position statement for Australian adults. Aust N Z J Public Health. 2024 Feb;48(1):100117. doi:10.1016/j.anzjph.2023.100117. https://pubmed.ncbi.nlm.nih.gov/38350754/
8. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008 Aug;88(2):582S-586S. doi:10.1093/ajcn/88.2.582S. https://pubmed.ncbi.nlm.nih.gov/18689406/
9. Gröber U, Spitz J, Reichrath J, Kisters K, Holick MF. Vitamin D: Update 2013: From rickets prophylaxis to general preventive healthcare. Dermatoendocrinol. 2013 Jun 1;5(3):331-47. doi:10.4161/derm.26738. https://pubmed.ncbi.nlm.nih.gov/24516687/
10. Maretzke F, Bechthold A, Egert S, Ernst JB, Melo van Lent D, *et al.* Role of Vitamin D in preventing and treating selected extraskeletal diseases - An Umbrella review. Nutrients. 2020 Mar 31;12(4):969. doi:10.3390/nu12040969. https://pubmed.ncbi.nlm.nih.gov/32244496/
11. Statistics Canada. Causes of death. https://www150.statcan.gc.ca/n1/daily-quotidien/230828/dq230828b-eng.htm

12. Dai L, Liu M, Chen L. Association of serum 25-hydroxyvitamin D concentrations with all-cause and cause-specific mortality among adult patients with existing cardiovascular disease. Front Nutr. 2021 Sep 23;8:740855. doi:10.3389/fnut.2021.740855. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8496747/

13. Entrenas Castillo M, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, López Miranda J, *et al.* Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol. 2020 Oct;203:105751. doi:10.1016/j.jsbmb.2020.105751. https://pubmed.ncbi.nlm.nih.gov/32871238/

14. McCullough PJ, Lehrer DS, Amend J. Daily oral dosing of vitamin D3 using 5000 TO 50,000 international units a day in long-term hospitalized patients: Insights from a seven year experience. J Steroid Biochem Mol Biol. 2019 May;189:228-239. doi:10.1016/j.jsbmb.2018.12.010. https://pubmed.ncbi.nlm.nih.gov/30611908/

15. Vieth R. Vitamin D toxicity, policy, and science. J Bone Miner Res. 2007 Dec;22 Suppl 2:V64-8. doi:10.1359/jbmr.07s221. https://pubmed.ncbi.nlm.nih.gov/18290725/ Other sources of information. https://pubmed.ncbi.nlm.nih.gov/18290725/

16. Religi A, Backes C, Chatelan A, Bulliard JL, Vuilleumier L, *et al.* Estimation of exposure durations for vitamin D production and sunburn risk in Switzerland. J Expo Sci Environ Epidemiol. 2019 Oct;29(6):742-752. doi: 10.1038/s41370-019-0137-2. Erratum in: J Expo Sci Environ Epidemiol. 2019 May 7. https://pubmed.ncbi.nlm.nih.gov/30992519/

17. Veugelers PJ, Ekwaru JP. A statistical error in the estimation of the recommended dietary allowance for vitamin D. Nutrients. 2014 Oct 20;6(10):4472-5. doi:10.3390/nu6104472. https://pubmed.ncbi.nlm.nih.gov/25333201/

18. Quraishi SA, Bittner EA, Blum L, Hutter MM, Camargo CA Jr. Association between preoperative 25-hydroxyvitamin D level and hospital-acquired infections following Roux-en-Y gastric bypass surgery. JAMA Surg. 2014 Feb;149(2):112-8. doi:10.1001/jamasurg.2013.3176. https://pubmed.ncbi.nlm.nih.gov/24284777/

19. Grant WB, Schwalfenberg GK, Genuis SJ, Whiting SJ. An estimate of the economic burden and premature deaths due to vitamin D deficiency in Canada. Mol Nutr Food Res. 2010 Aug;54(8):1172-81. doi:10.1002/mnfr.200900420. https://pubmed.ncbi.nlm.nih.gov/20352622/

20. National health expenditure trends, 2023. https://www.cihi.ca/en/national-health-expenditure-trends#Key-Findings

21. Alkundi A, Momoh R, Musa A, Nwafor N. Vitamin D intoxication and severe hypercalcaemia complicating nutritional supplements misuse. BMJ Case Rep. 2022 Jul 6;15(7):e250553. doi:10.1136/bcr-2022-250553. https://pubmed.ncbi.nlm.nih.gov/35793850/

22. Holick MF. Vitamin D Is not as toxic as was once thought: A Historical and an up-to-date Perspective. Mayo Clin Proc. 2015 May;90(5):561-4. doi:10.1016/j.mayocp.2015.03.015. https://pubmed.ncbi.nlm.nih.gov/25939933/

23. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS One. 2014 Nov 5;9(11):e111265. doi:10.1371/journal.pone.0111265. https://pubmed.ncbi.nlm.nih.gov/25372709/

24. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol. 2009 Feb;19(2):73-8. doi:10.1016/j.annepidem.2007.12.001. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2665033/

25. Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. Am J Clin Nutr. 2007 Jan;85(1):6-18. doi:10.1093/ajcn/85.1.6. https://pubmed.ncbi.nlm.nih.gov/17209171/

26. Wilson K. Rumbeiha DVM, PhD, DABVT, DABT, Cholecalciferol in small animal toxicology (Third Edition), 2013. https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/cholecalciferol

27. Kozioł-Kozakowska A, Maresz K. The impact of Vitamin K2 (Menaquionones) in children's health and diseases: A review of the literature. Children (Basel). 2022 Jan 5;9(1):78. doi:10.3390/children9010078. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8774117/

28. Dai L, Liu M, Chen L. Association of serum 25-hydroxyvitamin D concentrations with all-cause and cause-specific mortality among adult patients with existing cardiovascular disease. Front Nutr. 2021 Sep 23;8:740855. doi:10.3389/fnut.2021.740855. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8496747/

29. GBD 2016 Multiple Sclerosis Collaborators. Global, regional, and national burden of multiple sclerosis 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2019 Mar;18(3):269-285. doi:10.1016/S1474-4422(18)30443-5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6372756/

30. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. Mult Scler Relat Disord. 2017 May;14:35-45. doi:10.1016/j.msard.2017.03.014. https://pubmed.ncbi.nlm.nih.gov/28619429/

31. McLaughlin L, Clarke L, Khalilidehkordi E, Butzkueven H, Taylor B, Broadley SA. Vitamin D for the treatment of multiple sclerosis: a meta-analysis. J Neurol. 2018 Dec;265(12):2893-2905. doi:10.1007/s00415-018-9074-6. https://pubmed.ncbi.nlm.nih.gov/30284038/

32. Atkinson SA, Fleet JC. Canadian recommendations for vitamin D intake for persons affected by multiple sclerosis. J Steroid Biochem Mol Biol. 2020 May;199:105606. doi: 10.1016/j.jsbmb.2020.105606. https://pubmed.ncbi.nlm.nih.gov/31981800/

33. MS Canada. Vitamin D and MS. https://mscanada.ca/vitamin-d-multiple-sclerosis

34. Chandler PD, Chen WY, Ajala ON, Hazra A, Cook N, *et al.*; VITAL Research Group. Effect of vitamin D3 supplements on development of advanced cancer: A secondary analysis of the VITAL randomized clinical trial. JAMA Netw Open. 2020 Nov 2;3(11):e2025850.

doi:10.1001/jamanetworkopen.2020.25850. Erratum in: JAMA Netw Open. 2020 Dec 1;3(12):e2032460. https://pubmed.ncbi.nlm.nih.gov/33206192/

35. Wu E, Guo JP, Wang K, Xu HQ, Xie T, Tao L, Ni JT. Association of serum 25-hydroxyvitamin D with the incidence of 16 cancers, cancer mortality, and all-cause mortality among individuals with metabolic syndrome: a prospective cohort study. Eur J Nutr. 2023 Sep;62(6):2581-2592. doi:10.1007/s00394-023-03169-x. https://pubmed.ncbi.nlm.nih.gov/37209191/

36. Song ZY, Yao Q, Zhuo Z, Ma Z, Chen G. Circulating vitamin D level and mortality in prostate cancer patients: a dose-response meta-analysis. Endocr Connect. 2018 Dec 1;7(12):R294-R303. doi:10.1530/EC-18-0283. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6240137/

37. Zhou A, Selvanayagam JB, Hyppönen E. Non-linear Mendelian randomization analyses support a role for vitamin D deficiency in cardiovascular disease risk. Euro Heart J, 2022 May 7; 43(18) 1731–1739. https://doi.org/10.1093/eurheartj/ehab809

38. Tomaschitz A, Pilz S, Ritz E, Grammer T, Drechsler C, Boehm BO, März W. Independent association between 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D and the renin-angiotensin system: The Ludwigshafen Risk and Cardiovascular Health (LURIC) study. Clin Chim Acta. 2010 Sep 6;411(17-18):1354-60. doi:10.1016/j.cca.2010.05.037. https://pubmed.ncbi.nlm.nih.gov/20515678/

39. Yuan W, Pan W, Kong J, Zheng W, Szeto FL, *et al.* 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem. 2007 Oct 12;282(41):29821-30. doi:10.1074/jbc.M705495200. https://pubmed.ncbi.nlm.nih.gov/17690094/

40. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, *et al*. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. 2017 Feb 15;356:i6583. doi:10.1136/bmj.i6583. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5310969/

41. Borsche L, Glauner B, von Mendel J. COVID-19 mortality risk correlates inversely with vitamin D3 status, and a mortality rate close to zero could theoretically be achieved at 50 ng/mL 25(OH)D3: Results of a systematic review and meta-analysis. Nutrients. 2021 Oct 14;13(10):3596. doi:10.3390/nu13103596. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8541492/

42. Pinzon RT, Handayani T, Wijaya VO, Buana RB. Low vitamin D serum levels as risk factor of Alzheimer's disease: a systematic review and meta-analysis. Egypt J Neurol Psychiatry Neurosurg 59, 88 (2023). doi:10.1186/s41983-023-00676-w. https://ejnpn.springeropen.com/articles/10.1186/s41983-023-00676-w

43. Ghahremani M, Smith EE, Chen H-Y, Creese B, Goodarzi Z, Ismail Z. Vitamin D supplementation and incident dementia: Effects of sex, APOE, and baseline cognitive status. Alzheimer's Dement. 2023; 15:e12404. doi:10.1002/dad2.12404. https://alz-journals.onlinelibrary.wiley.com/doi/epdf/10.1002/dad2.12404

44. Pittas AG, Kawahara T, Jorde R, Dawson-Hughes B, Vickery EM, *et al.* Vitamin D and risk for Type 2 diabetes in people with prediabetes: A systematic review and meta-analysis of individual

participant data from 3 randomized clinical trials. Ann Intern Med. 2023 Mar;176(3):355-363. doi:10.7326/M22-3018. https://pubmed.ncbi.nlm.nih.gov/36745886/

45. Govani SM, Higgins PD, Stidham RW, Montain SJ, Waljee AK. Increased ultraviolet light exposure is associated with reduced risk of inpatient surgery among patients with Crohn's disease. J Crohns Colitis. 2015 Jan;9(1):77-81. doi:10.1093/ecco-jcc/jju002. https://pubmed.ncbi.nlm.nih.gov/25518047/

46. Alrefai (2017) The association of vitamin D status with disease activity in a cohort of Crohns disease patients in Canada. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5691728/

47. Wimalawansa SJ. Infections and autoimmunity-The immune system and Vitamin D: A systematic review. Nutrients. 2023 Sep 2;15(17):3842. doi:10.3390/nu15173842. https://pubmed.ncbi.nlm.nih.gov/37686873/

48. Fatahi S, Alyahyawi N, Albadawi N, Mardali F, Dara N, *et al*. The association between vitamin D status and inflammatory bowel disease among children and adolescents: A systematic review and meta-analysis. Front Nutr. 2023 Jan 9;9:1007725. doi:10.3389/fnut.2022.1007725. https://pubmed.ncbi.nlm.nih.gov/36698467/

49. Bendix M, Dige A, Jørgensen SP, Dahlerup JF, Bibby BM, *et al*. Seven weeks of high-dose vitamin D treatment reduces the need for Infliximab dose-escalation and decreases inflammatory markers in Crohn's disease during one-year follow-up. Nutrients. 2021 Mar 26;13(4):1083. doi:10.3390/nu13041083. https://pubmed.ncbi.nlm.nih.gov/33810258/

50. Berriche-Yahi N, Tahar A, Asselah H, Ayoub S, Hantala D, Koceir EA. Effets d'une supplémentation orale en vitamine D_3 chez des patients atteints de la maladie de Crohn: modulation des phases cliniques poussée/rémission par le profil cytokinique pro-inflammatoire et du stress oxydant [Effects of oral vitamin D_3 supplementation in Crohn's disease patients: Modulation of clinical active/remission phases by pro-inflammatory cytokines profile and oxidative stress]. Ann Biol Clin (Paris). 2022 Feb 1;80(1):29-46. French. doi:10.1684/abc.2021.1698. https://pubmed.ncbi.nlm.nih.gov/35129441/

51. Mehrani Y, Morovati S, Tieu S, Karimi N, Javadi H, *et al.* Vitamin D influences the activity of mast cells in allergic manifestations and potentiates their effector functions against pathogens. Cells. 2023 Sep 14;12(18):2271. doi:10.3390/cells12182271. https://pubmed.ncbi.nlm.nih.gov/37759494/

52. Lu H, Xie RD, Lin R, Zhang C, Xiao XJ, *et al*. Vitamin D-deficiency induces eosinophil spontaneous activation. Cell Immunol. 2017 Dec;322:56-63. doi:10.1016/j.cellimm.2017.10.003. https://pubmed.ncbi.nlm.nih.gov/29050663/

53. Wimalawansa SJ. Infections and autoimmunity-The immune system and vitamin D: A systematic review. Nutrients. 2023 Sep 2;15(17):3842. doi:10.3390/nu15173842. https://pubmed.ncbi.nlm.nih.gov/37686873/

54. Seraphin G, Rieger S, Hewison M, Capobianco E, Lisse TS. The impact of vitamin D on cancer: A mini review. J Steroid Biochem Mol Biol. 2023 Jul;231:106308. doi:10.1016/j.jsbmb.2023.106308. https://pubmed.ncbi.nlm.nih.gov/37054849/

55. Koivisto O, Hanel A, Carlberg C. Key Vitamin D Target Genes with Functions in the Immune System. Nutrients. 2020; 12(4):1140. doi:10.3390/nu12041140. https://www.mdpi.com/2072-6643/12/4/1140

56. Carlberg C. Genomic signaling of vitamin D. Steroids. 2023 Oct;198:109271. doi:10.1016/j.steroids.2023.109271. https://pubmed.ncbi.nlm.nih.gov/37442517/

57. Żmijewski MA. Nongenomic activities of vitamin D. Nutrients. 2022 Dec 1;14(23):5104. doi:10.3390/nu14235104. https://pubmed.ncbi.nlm.nih.gov/36501134/

58. Daryabor G, Gholijani N, Kahmini FR. A review of the critical role of vitamin D axis on the immune system. Exp Mol Pathol. 2023 Aug;132-133:104866. doi:10.1016/j.yexmp.2023.104866. https://pubmed.ncbi.nlm.nih.gov/37572961/

59. Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res. 2011 Jan;55(1):96-108. doi:10.1002/mnfr.201000174. https://pubmed.ncbi.nlm.nih.gov/20824663/

60. Amegah AK, Klevor MK, Wagner CL. Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: A systematic review and meta-analysis of longitudinal studies. PLoS One. 2017 Mar 17;12(3):e0173605. doi:10.1371/journal.pone.0173605. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5357015/

61. Mansur JL, Oliveri B, Giacoia E, Fusaro D, Costanzo PR. Vitamin D: Before, during and after pregnancy: Effect on neonates and children. Nutrients. 2022 May 1;14(9):1900. doi:10.3390/nu14091900. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9105305/

62. Drall KM, Field CJ, Haqq AM, de Souza RJ, Tun HM, *et al.* Vitamin D supplementation in pregnancy and early infancy in relation to gut microbiota composition and C. difficile colonization: implications for viral respiratory infections. Gut Microbes. 2020 Nov 9;12(1):1799734. doi:10.1080/19490976.2020.1799734. https://pubmed.ncbi.nlm.nih.gov/32779963/

63. Wu Y, Zeng Y, Zhang Q, Xiao X. The role of maternal vitamin D deficiency in offspring obesity: A narrative review. Nutrients. 2023 Jan 19;15(3):533. doi:10.3390/nu15030533. https://pubmed.ncbi.nlm.nih.gov/36771240/

64. Lisi G, Ribolsi M, Siracusano A, Niolu C. Maternal Vitamin D and its role in determining fetal origins of mental health. Curr Pharm Des. 2020;26(21):2497-2509. doi:10.2174/1381612826666200506093858. https://pubmed.ncbi.nlm.nih.gov/32370709/

65. https://www.grassrootshealth.net/document/disease-incidence-prevention-chart-in-ngml/

66. Głąbska D, Kołota A, Lachowicz K, Skolmowska D, Stachoń M, Guzek D. The influence of vitamin D intake and status on mental health in children: A systematic review. Nutrients. 2021 Mar

16;13(3):952. doi:10.3390/nu13030952. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7999324/

67. Guzek D, Kołota A, Lachowicz K, Skolmowska D, Stachoń M, Głąbska D. Association between vitamin D supplementation and mental health in healthy adults: A systematic review. J Clin Med. 2021 Nov 3;10(21):5156. doi:10.3390/jcm10215156. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8584834/

68. Foster BL, Nociti FH Jr, Somerman MJ. The rachitic tooth. Endocr Rev. 2014 Feb;35(1):1-34. doi:10.1210/er.2013-1009. https://pubmed.ncbi.nlm.nih.gov/23939820/

69. Foster BL, Nociti FH Jr, Somerman MJ. The rachitic tooth. Endocr Rev. 2014 Feb;35(1):1-34. doi:10.1210/er.2013-1009. https://pubmed.ncbi.nlm.nih.gov/23939820/

70. Botelho J, Machado V, Proença L, Delgado AS, Mendes JJ. Vitamin D deficiency and oral health: A comprehensive review. Nutrients. 2020 May 19;12(5):1471. doi:10.3390/nu12051471. https://pubmed.ncbi.nlm.nih.gov/32438644/

71. Nørrisgaard PE, Haubek D, Kühnisch J, Chawes BL, Stokholm J, *et al.* Association of high-dose vitamin D supplementation during pregnancy with the risk of enamel defects in offspring: A 6-year follow-up of a randomized clinical trial. JAMA Pediatr. 2019 Oct 1;173(10):924-930. doi:10.1001/jamapediatrics.2019.2545. https://pubmed.ncbi.nlm.nih.gov/31381020/

72. Botelho J, Machado V, Proença L, Delgado AS, Mendes JJ. Vitamin D deficiency and oral health: A comprehensive review. Nutrients. 2020 May 19;12(5):1471. doi:10.3390/nu12051471. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7285165/

73. Chapple IL, Bouchard P, Cagetti MG, Campus G, Carra MC, *et al.* Interaction of lifestyle, behaviour or systemic diseases with dental caries and periodontal diseases: consensus report of group 2 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal diseases. J Clin Periodontol. 2017 Mar;44 Suppl 18:S39-S51. doi:10.1111/jcpe.12685. https://pubmed.ncbi.nlm.nih.gov/28266114/

74. Dietrich T, Joshipura KJ, Dawson-Hughes B, Bischoff-Ferrari HA. Association between serum concentrations of 25-hydroxyvitamin D3 and periodontal disease in the US population. Am J Clin Nutr. 2004 Jul;80(1):108-13. doi:10.1093/ajcn/80.1.108. https://pubmed.ncbi.nlm.nih.gov/15213036/

75. Boggess KA, Espinola JA, Moss K, Beck J, Offenbacher S, Camargo CA Jr. Vitamin D status and periodontal disease among pregnant women. J Periodontol. 2011 Feb;82(2):195-200. doi:10.1902/jop.2010.100384. https://pubmed.ncbi.nlm.nih.gov/20809861/

76. Sllamniku Dalipi Z, Dragidella F. Calcium and vitamin D supplementation as non-surgical treatment for periodontal disease with a focus on female patients: Literature review. Dent J (Basel). 2022 Jul 1;10(7):120. doi:10.3390/dj10070120. https://pubmed.ncbi.nlm.nih.gov/35877394/

77. Kawakami M, Takano-Yamamoto T. Local injection of 1,25-dihydroxyvitamin D3 enhanced bone formation for tooth stabilization after experimental tooth movement in rats. J Bone Miner Metab. 2004;22(6):541-6. doi:10.1007/s00774-004-0521-3. https://pubmed.ncbi.nlm.nih.gov/15490263/

78. Lipworth L, Rossi M, McLaughlin JK, Negri E, Talamini R, *et al.* Dietary vitamin D and cancers of the oral cavity and esophagus. Ann Oncol. 2009 Sep;20(9):1576-1581. doi:10.1093/annonc/mdp036. https://pubmed.ncbi.nlm.nih.gov/19487490/

79. Bedogni A, Bettini G, Bedogni G, Basso D, Gatti D, *et al.* Is vitamin D deficiency a risk factor for osteonecrosis of the jaw in patients with cancer? A matched case-control study. J Craniomaxillofac Surg. 2019 Aug;47(8):1203-1208. doi:10.1016/j.jcms.2019.03.007. https://pubmed.ncbi.nlm.nih.gov/30929994/

80. Moneem Alhelfi N, Mohammed Hoobi, N. Effect of vitamin D deficiency on dental caries and salivary parameters. J Med Chem Sci. 2023; 6(6): 1362-1369. doi:0.26655/JMCHEMSCI.2023.6.16 https://www.jmchemsci.com/article_160715.html

81. Fábián TK, Hermann P, Beck A, Fejérdy P, Fábián G. Salivary defense proteins: their network and role in innate and acquired oral immunity. Int J Mol Sci. 2012;13(4):4295-4320. doi:10.3390/ijms13044295. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3344215/

82. Canadian Institute for Health Information. National health expenditure trends, 2023. https://www.cihi.ca/en/national-health-expenditure-trends#Key-Findings

Other resources.

MS Society. https://mscanada.ca/vitamin-d-multiple-sclerosis

Vitamin D Society. https://www.vitamindsociety.org

https://www.canadiansfortruth.ca/about-us

https://dgreatbiologyreset.com/ANDERSON-GRIMES-Vitamin-D3-and-the-Great-Biology-Reset-D3DE.pdf

Vitamin D testing. Test kits sold by ImmunoCeutica (https://immunoceutica.ca), Guelph, ON.