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# A Brief Overview on Vitamin D for Alaska Health Care Providers

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**Executive Summary**

This report aims to offer a brief overview of vitamin D for Alaska health care providers by a) reviewing the endogenous and dietary sources of vitamin D; b) discussing the well-established roles of vitamin D in the human body; c) summarizing dietary intake, supplementation, and screening recommendations that have been offered by selected professional and governmental bodies; d) describing the results of recent (mainly large-scale) studies looking into the potential roles of vitamin D outside of skeletal health; and e) summarizing Alaska-specific vitamin D research findings.

Vitamin D is an essential fat-soluble vitamin that is produced in the skin when ultraviolet sunlight contacts the skin and prompts vitamin D synthesis. It is also naturally present in some foods, such as oily fish (e.g., salmon, mackerel, and tuna). Vitamin D is best known for its role in promoting bone health by maintaining adequate levels of calcium and phosphorus to ensure proper bone metabolism. Vitamin D deficiency is known to cause bone disorders, including rickets in children and osteomalacia in adults. Recently, many observational studies and some clinical trials have shown associations between vitamin D deficiency and a growing list of adverse extraskeletal health outcomes; however, the results of most large-scale vitamin D clinical trials and meta-analyses of clinical trials to date have provided little support for many of the associations made in the aforesaid studies.

The absence of standardized cut-points for levels that confer vitamin D sufficiency has made it challenging to determine the prevalence of vitamin D deficiency, evaluate potential health outcomes, and provide informed recommendations for supplementation and screening. Although serum 25-hydroxyvitamin D concentration is the best available indicator of a person's vitamin D level, it is not clear how reliable this biomarker is for determining optimal vitamin D levels. Despite this uncertainty, many professional organizations have established vitamin D references values and intake and screening recommendations.

Epidemiologic studies suggest that the incidence of rickets has risen among Alaska Native children since the 1990s. While limited sunlight exposure and darker skin pigmentation are known risk factors for vitamin D deficiency, the recent changes in the diet of Alaska Native people appears to be an additional risk factor that may be contributing to the increased incidence of rickets among Alaska Native children. Additional studies will help characterize the extent of vitamin D deficiency and its health consequences in Alaska, determine the importance of traditional foods in maintaining vitamin D sufficiency among Alaska Native people, and determine the differential vitamin D intake (i.e., food/supplementation) needs among people of differing latitudes and skin pigmentations. In the meantime, anyone who lives in Alaska and thinks they are not getting enough vitamin D through sunlight exposure and their diet should talk with their health care provider about supplementation. During the darker months of winter, Alaskans can assume that they are getting very little (if any) vitamin D from local sunlight exposure.

In conclusion, Alaska health care providers' decisions about screening and offering supplementation recommendations for their patients should be informed by a balanced perspective of their patients' unique risk factors for vitamin D deficiency (e.g., limited exposure to sunlight, having darker skin pigmentation, and insufficient dietary intake) and the currently available clinical guidelines disseminated by respected professional and governmental bodies. For example, the Institute of Medicine and the U.S. Preventive Services Task Force have provided broad guidance on the topic, and other bodies such as the American Congress of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the American Geriatrics Society have provided guidance that is more specific to selected populations. Lastly, while vitamin D supplements appear to be safe at recommended doses, the Institute of Medicine has established tolerable upper intake levels for vitamin D, which are set at 4,000 International Units per day for persons aged ≥9 years, and lower levels for younger children.

## Introduction

Vitamin D is an essential fat-soluble vitamin that is primarily responsible for maintaining normal serum concentrations of calcium and phosphate by increasing their absorption in the small intestine. Vitamin D deficiency is known to cause demineralization of bones and other tissues, leading to skeletal problems such as osteomalacia and rickets. Over the past decade, there has been growing interest and research regarding the role of vitamin D deficiency in non-skeletal health. This interest has been prompted in part by the fact that vitamin D receptors have been found on a wide range of cell types in the human body, and many of these cells have enzymes that convert vitamin D from its inert form to its active form.[1]

Because most of the vitamin D in the human body is typically synthesized endogenously by way of dermal exposure to ultraviolet light, living in far northern or southern latitudes is a known risk factor for vitamin D deficiency. As such, Alaska health care providers should be knowledgeable about vitamin D to educate their patients on risk factors for vitamin D deficiency and help them make informed decisions regarding vitamin D intake and supplementation. The purpose of this *Bulletin* is to provide a general overview of the state of the science on vitamin D and to summarize dietary intake, supplementation, and screening recommendations that have been offered by selected professional and governmental bodies.

## Part I. BACKGROUND

### Sources, Metabolism, and Roles of Vitamin D

Humans synthesize vitamin D upon exposure to ultraviolet B (UVB) light; up to 80–90% of vitamin D is endogenously synthesized in the skin.[2] Very few natural dietary sources are rich in vitamin D; notable exceptions to this include fatty fish, fish oil, and marine mammal fats and organs (e.g. liver).[3] The rest of our dietary vitamin D intake comes from fortified foods like milk and cereal or dietary supplements.

There are two forms of vitamin D available in fortified foods and over-the-counter supplements--vitamin $D_2$ and vitamin $D_3$, known as ergocalciferol and cholecalciferol, respectively. Vitamin $D_3$ is considered the "natural" form of vitamin D as it is the primary form found in foods and synthesized in the skin upon exposure to UVB light. The vitamin $D_3$ offered in nutritional supplements is most commonly produced by UVB irradiation of an extract of lanolin derived from sheep's wool.[4] Vitamin $D_2$, on the other hand, is manufactured by exposing ergosterol from yeast to UVB light. Supplements of both forms effectively raise serum 25(OH)D concentrations (which represents the combined sum of 25(OH)$D_2$ and 25(OH)$D_3$ concentrations).[5] Accumulating evidence suggests that the pharmacokinetic properties of vitamin $D_3$ and vitamin $D_2$ change with dosage level. At lower doses, vitamin $D_2$ and $D_3$ appear to have similar effects in elevating or maintaining total serum 25(OH)D concentrations; however, numerous studies have shown vitamin $D_2$ to be less effective in elevating or maintaining total serum 25(OH)D levels at higher doses.[4,5]

The form of vitamin D that originates from the diet, supplements, or sun exposure is biologically inert, and thus must undergo two hydroxylation steps before it can be utilized in physiologic processes (Figure). The first hydroxylation step occurs in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25[OH]D), the main circulating and stored form of the vitamin.

When vitamin D is required for physiological needs, like maintaining calcium and phosphorus homeostasis, 25(OH)D is hydroxylated, mainly in the kidneys, to its hormonally active form 1,25-dihydroxyvitamin D (1,25$[OH]_2$D).[5]

Vitamin D promotes calcium absorption in the gut and maintains homeostatic levels of calcium and phosphate needed for proper bone mineralization and remodeling.[5] Less understood functions that vitamin D may play in the body include modulation of cell growth, maintenance of proper neuromuscular and immune function, and reduction of inflammation.[6,7] More generally, vitamin D has also been shown to modulate cell proliferation, differentiation, and apoptosis.[1,8] The translation of these roles into health outcomes is not yet well established.

The connection between vitamin D and skeletal health has long been understood. Historically, vitamin D deficiency was defined as the presence of signs and symptoms compatible with rickets in children and osteomalacia in adults.[2] Both conditions are caused by defective mineralization of the skeleton, with rickets first being recognized in the late 19$^{th}$ century when children started presenting with spinal deformities, knobby projections on their ribs, and bowed legs.[6] After vitamin D-fortified milk was introduced in the 1930s, the incidence of rickets in children decreased substantially, further supporting the connection between vitamin D and this childhood condition. Similar to rickets, numerous studies have linked low serum concentrations of 25(OH)D to the increased risk of osteomalacia and osteoporosis-related fractures and falls in adults.[9–12]

While the focus of vitamin D deficiency research has historically centered on conditions that result from improper bone development, investigations into vitamin D's potential non-skeletal functions are expanding. This is partly due to the finding that vitamin D receptors appear on cells other than enterocytes and osteoblasts, like lymphocytes, colon cells, pituitary gland cells, and ovarian cells.[1,3] In recent years, there has been a surge in research on the potential connection between vitamin D and several types of cancer, diabetes, cardiovascular diseases, autoimmune diseases, infectious diseases (e.g., tuberculosis), and pregnancy outcomes (e.g., preeclampsia and preterm birth).[6,13-15] This swell in vitamin D research has also generated interest in more precisely determining optimal serum vitamin D concentrations and refining screening and supplementation recommendations.[16]

**Vitamin D Testing**

The most common indicator of vitamin D status is serum 25(OH)D concentration because:[2,16]

- it is the major circulating form of vitamin D;
- it is the most stable (15 day half-life);
- it is an accurate indicator of the combined product of synthesis from UVB exposure and dietary intake; and
- serum 25(OH)D concentrations correlate with rickets and other clinical diseases.[5,17,18]

The more active form of vitamin D, 1,25$(OH)_2$D, is generally not used to indicate vitamin D status because it typically does not decrease until vitamin D deficiency is severe and is tightly regulated by certain hormones and serum calcium and phosphorus levels.[1,16] Although 25(OH)D concentrations are the best marker for vitamin D status, clinicians should account for several confounding factors affecting serum 25(OH)D concentrations, including

the time of year, dietary calcium intake, skin pigmentation, latitude, and medications that alter vitamin D metabolism.[7,19,20] In addition, serum 25(OH)D concentrations do not represent the total bioavailable 25(OH)D, which can be stored in other tissues (mainly fats). This has been demonstrated by several studies that have shown increased 25(OH)D concentrations after moderate weight loss.[7]

The most common testing methods for vitamin D status are measurement of serum 25(OH)D using either antibody-based or liquid chromatography-based assays.[21] Unfortunately, variability between assay methods and laboratories as well as the absence of distinct cut-points can result in different classifications of samples as either deficient or not deficient. While serum 25(OH)D is currently respected as the best available indicator of vitamin D exposure, it is not clear to what extent the level serves as a biomarker of health status or effect.[5]

**National Prevalence of Vitamin D Deficiency**

Owing to the lack of consensus on how to define and assess vitamin D deficiency, establishing prevalence estimates is complicated. Even with the Institute of Medicine (IOM) reference levels for vitamin D concentrations, there can be misinterpretation or misapplication of the values.[19] In addition, reference levels do not apply universally and there exists the biological reality that the need for vitamin D, like any nutrient, will vary from person to person. The Centers for Disease Control and Prevention (CDC) has been comprehensively assessing vitamin D status since the 1988–1994 National Health and Nutritional Examination Survey III (NHANES III). In 1999, NHANES was redesigned to become a continuous rather than periodic survey, releasing data every 2 years. Unfortunately, methods for 25(OH)D measurement changed twice from NHANES III to NHANES 2007–2010, complicating attempts to analyze trends.[22]

Despite this, one study compiled NHANES data from 1988–2010, estimating that 14%–18% of the U.S. population aged ≥12 years had a concentration of 25(OH)D <40 nmol/L,[23] which is the concentration consistent with an intake equivalent to IOM's Estimated Average Requirement (EAR).[7] However, when the data were stratified for race/ethnicity, the proportion of persons with 25(OH)D <40 nmol/L was 46%–60% for non-Hispanic blacks, 21%–28% for Hispanic, and 6%–10% for non-Hispanic whites.[23]

Similarly, a National Center for Health Statistics review of NHANES data for 2001–2006 showed that 24% of the population had serum 25(OH)D values between 30–49 nmol/L (i.e., inadequate; Table 1) and 8% had levels <30 nmol/L (i.e., deficient; Table 1). They also found that the prevalence of vitamin D deficiency was highest for non-Hispanic blacks, followed by Hispanic, and non-Hispanic whites (32%, 9%, and 3%, respectively).[24] Another study showed that over 80% of black adults are at risk for vitamin D insufficiency (25[OH]D concentration <50 nmol/L).[25] Lastly, there was a lower prevalence of vitamin D deficiency among males compared to females across both study years and age groups; the lowest prevalence (1%) of vitamin D deficiency in both sexes was in children aged 1–8 years.[23,24]

Lastly, studies of U.S. prison populations have shown that rates of vitamin D deficiency among inmates may be higher than the general population.[26,27] One study in particular found that out of 59 inmates, 38 (64%) were vitamin D deficient or

insufficient (per the 2011 IOM definitions of deficiency and insufficiency),[26] which is more than double the national rate of vitamin D deficiency or insufficiency (32%, per the 2011 IOM definitions).[7,24] Another study of 526 inmates found that when stratified by race, a greater percentage of Black inmates were found to be vitamin D insufficient compared to White inmates, 51% and 29% respectively.[27] This is similar to the racial patterns seen in the general U.S. population discussed above.[23-25] While most prison systems have uniform nutritional guidelines for all inmates, variability in vitamin D status is possible due to factors such as skin pigmentation, seasons, and the incarceration security level. Moreover, a high prevalence of vitamin D insufficiency in prison populations could also be a marker for poorer health status overall in these populations.[28] More comprehensive analyses of the vitamin D status among prison inmates are warranted.

**National Dietary Intake, Supplementation, and Screening Recommendations**

The indeterminacy of vitamin D cut-points and laboratory assessment methods have made it difficult to determine appropriate vitamin D intake amounts. However, in 2011, the IOM established reference values based on the current scientific evidence to better protect the public's health and help practitioners make more informed decisions regarding vitamin D supplementation.[7] While some organizations quote different reference levels, the IOM is well cited and referenced by most respected professional and governmental bodies.

*Institute of Medicine*

In 2011, the IOM (now the National Academy of Medicine) released a revised version of their 1997 report on vitamin D and calcium requirements, which provides updated cut points (Table 1) and Dietary Reference Intakes (DRIs; Table 2). DRIs are intended for public health applications and therefore use health outcomes as indicators for estimating a nutrient requirement. The DRIs for vitamin D represent the daily dietary intake that is considered sufficient to maintain bone health and normal calcium metabolism in healthy persons, assuming minimal sunlight exposure. The IOM commented that the potential roles of vitamin D outside skeletal health are best described as hypotheses of emerging interest and cannot be used to establish DRI reference values. Specific to life stage, age group, and sex, DRIs are categorized into the following components: Adequate Intake (AI) level, Estimated Average Requirement (EAR), Recommended Daily Allowance (RDA), and Tolerable Upper Intake Level (UL; Tables 2 and 3).[7]

The DRI components for each life-stage and age group include an estimated intake level that meets the needs of 50% of the population (EAR) as well as an estimated intake level that meets the needs of 97.5% of the population (RDA), and an upper level of intake to ensure no adverse health effects from nutrient intake (UL). The UL should not be used as a recommended level of intake, but rather viewed as the highest intake level that can be tolerated without causing adverse health effects. Adequate intakes (AI) are only calculated when the evidence base is insufficient to calculate EARs and RDAs.

Lastly, the committee concluded that 50 nmol/L (20 ng/mL) is the 25(OH)D serum concentration that protects 97.5% of the population from the adverse health effects of vitamin D deficiency (i.e., rickets and osteomalacia), as maximal calcium absorption is seen between vitamin D concentrations of 30–50 nmol/L (12–20

ng/mL), with little evidence of further benefit beyond 50 nmol/L.[7,29] The calculated RDA is the suggested intake needed to maintain a level of 50 nmol/L (Table 3). For more information on development of vitamin D DRIs, refer to the IOM report.[7]

For obvious ethical reasons, no systematic study has examined vitamin D toxicity in humans; therefore, anecdotal vitamin D intoxication reports provide the only human data for recommended upper limits (ULs).[18] However, researchers have conducted several animal studies involving systematic vitamin D intoxication, which allowed investigators to study when and why toxicity occurs. Rodents were able to tolerate 25(OH)D concentrations in the range 250–1000 nmol/L (100–400 ng/mL).[30,31]

In humans, serum 25(OH)D concentrations >500–600 nmol/L (200–240 ng/mL) are considered toxic; such concentrations have been shown to occur at vitamin D doses >10,000 IU/day.[32] However, ULs for vitamin D supplementation serve the purpose of protection over a lifetime of chronic intake, not just the avoidance of acute toxicity or hypercalcemia.[33] Some studies indicate that serum 25(OH)D concentrations >125 nmol/L (50 ng/mL) might result in adverse health outcomes.[7,33] Moreover, no health benefits have been confirmed at serum 25(OH)D concentrations >75 nmol/L (30 ng/mL).[7,33] As such, the IOM committee determined that the UL should reflect a more conservative dose than current toxicity reports indicate, and take into account the variability in individual dose-response (Table 3).[7]

*Other Recommendations*

Many other nationally respected scientific and health care bodies have issued their own vitamin D intake, supplementation, or screening statements relevant to the populations they represent. Most are largely in agreement with the IOM recommendations (Table 4).[21,34-42]

*Supplementation Precautions*

Vitamin D supplements at recommended doses are safe and are available without a health care provider's prescription. However, it is important to note that, although vitamin D intoxication is rare, ingestion of excessively high levels of vitamin D can lead to non-specific symptoms such as weight loss, polyuria, and heart arrhythmias, as well as more severe conditions like hypercalcemia, which leads to vascular and tissue calcification.[43,44] Persons with certain medical conditions such as hypercalcemia, hyperphosphatemia, and granulomatous conditions should consult with their health care provider before taking vitamin D supplements.[44] In addition, individuals taking corticosteroids, orlistat, certain cholesterol-lowering drugs (e.g., Questran®, LoCholest®, and Prevalite®), and certain seizure medications (e.g., phenobarbital and phenytoin) should consult with their health care providers before taking vitamin D supplements, which have the potential to interact with these medications by reducing calcium absorption and vitamin D metabolism and absorption.[43]

## PART II. CURRENT RESARCH ON NON-SKELETAL EFFECTS OF VITAMIN D DEFICIENCY

### Methods

We conducted a literature search with a combination of convenience and snowball sampling. We started with a meta-analysis of meta-analyses from 2014, which reviewed 107 systematic reviews, 74 meta-analyses of observational studies (48 non-overlapping meta-analyses), and 87 meta-analyses of randomized clinical trials (RCTs; 57 non-overlapping meta-analyses) evaluating vitamin D and 137 health outcomes.[44] This study referred us to other well-cited meta-analyses from reputable journals that either performed broad literature reviews of vitamin D and multiple health outcomes or more narrow reviews looking at vitamin D and specific health outcomes of interest (e.g., cardiovascular disease, diabetes, preterm birth and preeclampsia, and/or cancer). In parallel, we searched for the most recent studies and meta-analyses (from 2014-present) on key health outcomes of interest. Findings from reliable and well-cited studies were recorded and summarized.

### Results

Vitamin D is increasingly implicated in many diseases outside of the musculoskeletal system, but the available research studies are often inconsistent. Data from observational studies have demonstrated associations between low vitamin D levels and increased risk for cancer, cardiovascular disease, diabetes, autoimmune diseases, preeclampsia and gestational diabetes, and all-cause mortality.[12,13,28,46-48] The list of potential associations continues to grow as more research is directed at the effects of vitamin D in the body. Given the breadth of scientific literature, a summary of all studies cannot be concisely laid out here.

*Disease-specific Outcomes*

The largescale review of meta-analyses (described in the methods section above) explored the relationship between vitamin D and 137 outcomes ranging from many types of cancer to specific infectious diseases.[45] They identified 74 meta-analyses of observational studies with 48 non-overlapping meta-analyses. The number of studies included in each systematic review or meta-analyses ranged from 1–38 and only 10 of the 137 outcomes were measured by both meta-analyses of observational studies and meta-analyses of RCTs. Of those 10 outcomes, the direction of association and level of statistical significance was only concordant for birth weight. The 87 meta-analyses of RCTs (with 57 non-overlapping meta-analyses), assessing vitamin D supplementation and risk of disease, failed to confirm other associations suggested from the meta-analyses of observational studies. A "probable" association was identified between vitamin D concentrations and birth weight, dental caries in children, maternal vitamin D concentrations at term, and parathyroid hormone concentrations in patients with chronic kidney disease requiring dialysis, and a "suggestive" association was identified for a number of other health outcomes including colorectal cancer and cardiovascular disease.[45] However, the authors emphasized that they did not find convincing evidence of a clear role of vitamin D in any of these outcomes.[45]

The discrepancy between the findings of observational studies and RCTs has been reported in other meta-analyses where prospective studies reported inverse associations between 25(OH)D concentrations and multiple health

conditions, while vitamin D intervention studies showed little to no effect on those disorders.[28] Many meta-analyses of disease-specific studies including CVD, metabolic disorders, and cancer also could not confirm associations found in previous observational studies.[49-52] A recent meta-analysis of vitamin D supplementation for prevention of acute respiratory tract infections provided evidence for the protection against such conditions among all participants (OR 0.88, 95% CI 0.81–0.96).[53] Despite the small but statistically significant reduction in overall risk, the authors did not conclude with recommendations for changes to clinical practice or vitamin D supplementation. A recent RCT examined the effect of vitamin D supplementation on viral upper respiratory tract infections in young children, and found that high-dose vitamin D supplementation did not prevent or reduce overall upper respiratory tract infections in the study subjects.[54]

*All-cause Mortality*

Some meta-analyses have simply looked at the association between all-cause mortality and vitamin D status. Their findings suggest that individuals with lower baseline circulating 25(OH)D concentrations have a greater risk of all-cause mortality.[13,48,55] However, these findings are not universal. Other large meta-analyses of cohort studies and RCTs found marginal to no reduction in risk of death with vitamin D supplementation.[28,56] In fact, some research has been clear to point out that more is not always better when it comes to vitamin D concentrations.[57] In several instances, increased mortality has been seen at the highest serum 25(OH)D concentrations, indicating that vitamin D can be harmful at higher exposure levels.[7]

*Limitations*

Meta-analyses allow for a broad assessment of the current literature. They are able to place current studies in the context of previous studies in order to estimate an average effect across studies or identify differences among study-specific effects.[55] However, meta-analyses depend strongly on the quality and quantity of studies included. For example, some health related outcomes are not as robustly studied as others, creating gaps in the research. Similarly, there are relatively small numbers of trials for each intervention approach, such as dosage, duration, and follow-up time.[13] In addition, meta-analyses are subject to publication bias, most commonly significance bias, which is the tendency of investigators and editors to preferentially report and accept associations that are either novel or statistically significant.[58] Lastly, the inability to uniformly measure vitamin D exposure because of the absence of standardized laboratory measurements and vitamin D status cut-points limits comparisons of vitamin D concentrations and associated health outcomes across studies.

**Discussion**

Current RCTs have been unable to systematically and convincingly confirm the benefits of supplementation, suggesting that low 25(OH)D might be a marker of ill health rather than the cause of it. It has been hypothesized that inflammation is the common factor between most non-skeletal health disorders and low 25(OH)D concentrations.[28] Therefore, the inflammatory process involved in the progression of many diseases would be part of the reason we see reductions in 25(OH)D concentration and only the treatment of these disorders would be followed by increase in 25(OH)D concentrations. This again suggests that vitamin D status could

be a biological marker of deteriorating health, not the cause of it.

Despite the discrepancies between observational studies and RCTs and the conflicting results within these study designs, it is important to recognize that even small gains in prevention can be impactful from a population-based public health perspective. Associations from observational studies and RCTs have prompted refined vitamin D recommendations and provided new avenues for future research. Multiple large-scale vitamin D intervention trials have been launched globally with results expected in the upcoming years.[59,60] One such study of particular interest is the VITAL (*VIT*amin D and Omeg*A*-3 Tria*L*) study, a large clinical trial with over 25,000 participants that aims at assessing the roles of vitamin D and omega-3 fatty acid supplementation in the prevention of cancer and CVD. The preliminary results of this study are expected to be available by 2018 (see: http://www.vitalstudy.org/).

Lastly, a new RCT was recently published that evaluated the effect of supplementation with vitamin D and calcium on the risk of all-type cancer in postmenopausal women.[61] They concluded that supplementation did not result in a reduced risk of all-type cancer. Interestingly, a previous, smaller RCT by the same lead author, which followed an analogous study design, produced very different results.[62] The earlier study found a 60% reduction in all-type cancer incidence after vitamin D and calcium supplementation.[62] As such, more studies in diverse populations using standardized assessment methodologies will be needed before clear recommendations can be expected to emerge from respected national scientific bodies such as the Institute of Medicine and the U.S. Preventive Services Task Force.

## Part III. VITAMIN D DEFICIENCY IN ALASKA

### Methods

For literature specific to Alaska, we searched PubMed for articles published in English from inception to present day. We used the search terms "vitamin D", "Alaska", and "rickets", which yielded 22 articles. Studies that were not focused on humans and were not completed in Alaska populations were excluded, resulting in nine articles from 1997–2016. Ongoing studies were not included.

### Results

Due to our far northern latitude, vitamin D deficiency is an issue of public health interest and ongoing research in Alaska and other Arctic populations.[16]

*Epidemiology of Rickets and Vitamin D Deficiency in Alaska Children*

Reports of rickets in Alaska children increased in the 1990s.[63,64] Case histories were presented in the *Alaska Medicine* journal and identified all childhood rickets cases to be in Alaska Native or African American children, underscoring the potential connection between skin pigmentation and endogenous vitamin D synthesis.[64] However, it was not until more recently that studies on the epidemiology of rickets and vitamin D deficiency in Alaska Native children were conducted.

A study published in 2015 found that during 2001–2010, Alaska Native children had higher average annual rates of rickets and vitamin D-associated hospitalizations than the general U.S. pediatric population and American Indian children from all other Indian Health Service (IHS) facilities.[65] The incidence of rickets increased with latitude. Moreover, the absence of vitamin D supplementation during the first 6 months of life was associated with vitamin D deficiency and subsequent development of rickets in Alaska Native children, regardless of their breastfeeding status.[65] These findings add to the body of evidence in support of supplementing all breast-fed and formula-fed infants with vitamin D, as is recommended by the American Academy of Pediatrics.

When analyzing trends in vitamin D deficiency and rickets, the 2015 study noted an increase in vitamin D deficiency (but not rickets) cases in the late period (2006–2013) compared to the early period (1999–2005). The authors hypothesized that increased scientific reports on vitamin D deficiency may have led to greater provider awareness and higher vitamin D screening rates in Alaska Native children (see: http://www.epi.alaska.gov/bulletins/docs/b2014_06.pdf).[65]

*Dietary Changes, Age, and Serum 25(OH)D Concentrations in Alaska Native People*

Additionally, there are strong correlations between serum 25(OH)D concentrations and age in Alaska Native populations, with younger age demographics being at greater risk for low vitamin D levels.[66–69] A study of vitamin D samples from a Tribal Health clinic in Ketchikan found that 89% of serum samples were deficient in vitamin D, where the average age of participants in the lowest quartile of serum vitamin D levels was 14.6 years younger than the highest quartile.[68] One proposed explanation is the dietary transition from traditional foods to more store-bought foods, especially among younger generations.

Traditional Alaska Native diets are high in vitamin D.[3,69] One study of Alaska Yup'ik people demonstrated that despite low levels of sun exposure, circulating 25(OH)D concentration was within the recommended optimal range.[70] The authors suggest that

genetic adaptations and the high vitamin D content found in traditional foods may maintain adequate concentrations of serum 25(OH)D. Further evidence for this comes from studies that demonstrate positive associations between biomarkers of a traditional marine diet and increased serum 25(OH)D concentrations with the highest levels found in older age demographics.[66-68]

More specifically, a study of women of childbearing age from the Yukon-Kuskokwim Delta region concluded that a main contributor to the decline in serum 25(OH)D concentrations between the 1980s and 2010s was the sharp decrease in traditional marine food intake in these women during the 1960s through the 1990s.[71] It is possible that this dietary transition in women also contributed to the high incidence of rickets in Alaska Native children since the 1990s.[63,65] Moreover, many studies conclude with recommendations for pre- and post-natal supplementation of all mothers and infants, regardless of the mother's vitamin D status.[36,37,65,72,73]

Some studies involving other indigenous populations in the Arctic and sub-Arctic have shown a marked decline in serum 25(OH)D among all age-groups starting from the late 1980s through the 2000s.[72,74] Like Alaska Native populations, the younger generation tends to have lower 25(OH)D serum concentrations compared to older age groups, possibly indicating a generational movement away from traditional lifestyles to a more "westernized" way of life.[74,75] This could indicate that traditional foods were historically responsible for maintaining adequate levels of vitamin D among indigenous populations in the north, rather than sunlight.

*Limitations*

Many of the randomly selected populations may not be representative of the population as a whole, as the sampling methods were limited in size, geographic scope, and other potentially important environmental and demographic characteristics. For instance, one of the studies focused on WIC clinics in Alaska, which may only represent children who have relatively low socioeconomic status and may eat fewer foods rich in vitamin D.[63] Finally, the analysis of visit rates and clinical information is dependent on documentation of ICD codes of laboratory and clinical data, feeding, and vitamin D supplementation in electronic medical records and charts. Lack of documentation of vitamin D supplementation does not necessarily correlate with supplementation not having occurred among study subjects.

While a comprehensive literature search was completed for studies in Alaska, the majority are epidemiological, retrospective, and/or observational. Currently, no RCTs have been completed in Alaska and therefore definitive conclusions about the health effects of vitamin D in Alaska cannot be drawn from the current studies.

**Discussion**

In summary, these studies identify northern latitude, skin pigmentation, lack of vitamin D supplementation, breast-feeding without supplementation, and the shift away from traditional diets as risk factors for vitamin D deficiency. Most of these risk factors have been previously characterized in a number of studies.[63-65,73,76-78] For example, one review of 65 cases of nutritional rickets (reported during 1975–1985 in 11 publications) found that 91% of rickets cases were among black children aged 2–45 months; all of these children were either breast-fed or consumed a milk-free

vegetarian diet.[79] Similarly, another review of 166 cases of nutritional rickets (among patients aged 4–54 months reported during 1986–2003 in 22 publications) found that 83% of patients were described as black and 96% were breast-fed. Of those who were breast-fed, only 5% received vitamin D supplementation.[78] Additionally, only five of the 22 studies reported cases among white children. All white children were from the northern U.S.[78] These findings substantiate the findings from studies in Alaska that showed increased rates of rickets among persons living in higher latitudes and those with darker skin pigmentation. The studies also found increased prevalence of low serum 25(OH)D levels in infants who were breast-fed in the absence of vitamin D supplementation.[63-65]

One risk factor for vitamin D deficiency listed above that has been more recently characterized is the shift away from local and traditional foods to a store-bought diet. One article notes that decreased dietary intake in certain populations may arise from choice or necessity as is the case in poorer neighborhoods that may be unable to afford foods rich in vitamin D (or vitamin D fortified foods).[78] More generally, there are limited natural sources of vitamin D in foods, making it difficult for many people to consume adequate amounts of vitamin D in their diet.

Traditional Alaska Native foods such as marine mammals and oily fish are rich in vitamin D, and higher serum concentrations of 25(OH)D tend to be seen more commonly in older Alaska Native people due to the practice of a traditional lifestyle and culture.[5,66,67] One study demonstrated relatively high mean serum 25(OH)D concentrations, especially in older individuals, during both the summer and winter months in the Yukon Kuskokwim Delta, likely due to more persistent subsistence and cultural practices.[67]

The consistent observation of skin pigmentation, limited sun exposure, breast-feeding in the absence of supplementation, and now changes in dietary patterns as risk factors for vitamin D deficiency may warrant more focus on how to mitigate these risks through dietary intervention or supplementation. This becomes especially important for Alaska Native children who experience almost double the rate of rickets compared to the general U.S. pediatric population. As noted in *Alaska Medicine* in 1997, it may be an "oversimplification" to have universal recommendations for vitamin D screening and supplementation across all demographic groups nationally, as there is differential risk in disparate populations.[80]

## Part IV. CONCLUSION

Vitamin D receptors are found on almost every cell type in the human body, raising questions about whether vitamin D may play a role in a wider range of biological processes than we currently understand. In fact, many observational studies and some clinical trials have shown associations between vitamin D deficiency and a growing list of extraskeletal adverse health outcomes; however, the results of most large-scale vitamin D supplementation clinical trials and meta-analyses of clinical trials to date have provided little support for many of the associations made in the aforementioned studies.

Some of the key theories that offer counterarguments to proponents of increased vitamin D supplementation are worth noting. First, adequate serum 25(OH)D concentrations may be a result of good health and associated health practices (e.g., more time outdoors, more physical activity, and better diets), which may be limited in states of ill-health. Second, persons consuming a traditional diet might be exposed to more beneficial nutrients such as iron and omega-3 fatty acids that could confound studies investigating direct connections between dietary vitamin D and health outcomes. Lastly, the association between northern latitude and certain adverse health outcomes (e.g., certain cancers and multiple sclerosis) may be related to benefits of sun exposure that have not yet been identified.[60]

Additional studies will help characterize the extent of vitamin D deficiency and its health consequences in Alaska, determine the importance of traditional foods in maintaining vitamin D sufficiency among Alaska Native people, and determine the differential vitamin D intake (i.e., food/supplementation) needs among people of differing latitudes and skin pigmentations. In the meantime, anyone who lives in Alaska and thinks they are not getting enough vitamin D through sunlight exposure and their diet should talk with their health care provider about supplementation. During the darker months of winter, Alaskans can assume that they are getting very little (if any) vitamin D from local sunlight exposure.[76]

It is important to note that while this *Bulletin* presents an overview of the current knowledge surrounding vitamin D research and key health outcomes, this was not a complete systematic literature review and not all studies were captured by the selected RCTs and meta-analyses. The presented results were driven by key health outcomes that do not represent the complete list of health outcomes associated with vitamin D deficiency characterized in the literature. This report is also susceptible to the limitations of the individual studies and meta-analyses selected.

Alaska health care providers' decisions about vitamin D screening and supplementation recommendations for their patients should be informed by a balanced perspective of their patients' unique risk factors for vitamin D deficiency (e.g., limited exposure to sunlight, having darker skin pigmentation, and insufficient dietary intake) and the currently available clinical guidelines disseminated by respected professional and governmental bodies. For example, the American Congress of Obstetricians and Gynecologists' has provided recommendations (beyond the IOM RDAs and the USPSTF recommendations) for screening pregnant women thought to be at increased risk for vitamin D deficiency, which includes women residing at high northern latitudes

(defined as a region where >50% of the population lives at >58˚ N) and certain ethnic minorities (e.g., people with darker skin pigmentation). Moreover, the American Academy of Pediatrics and the American Geriatrics Society have issued specific vitamin D supplementation recommendations that pertain to infants and seniors (Table 4). Lastly, while vitamin D supplements appear to be safe at recommended doses, IOM has established tolerable upper intake levels for vitamin D, which are set at 4,000 International Units per day for persons aged ≥9 years, and lower levels for younger children (Table 3).

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## APPENDIX OF FIGURES AND TABLES

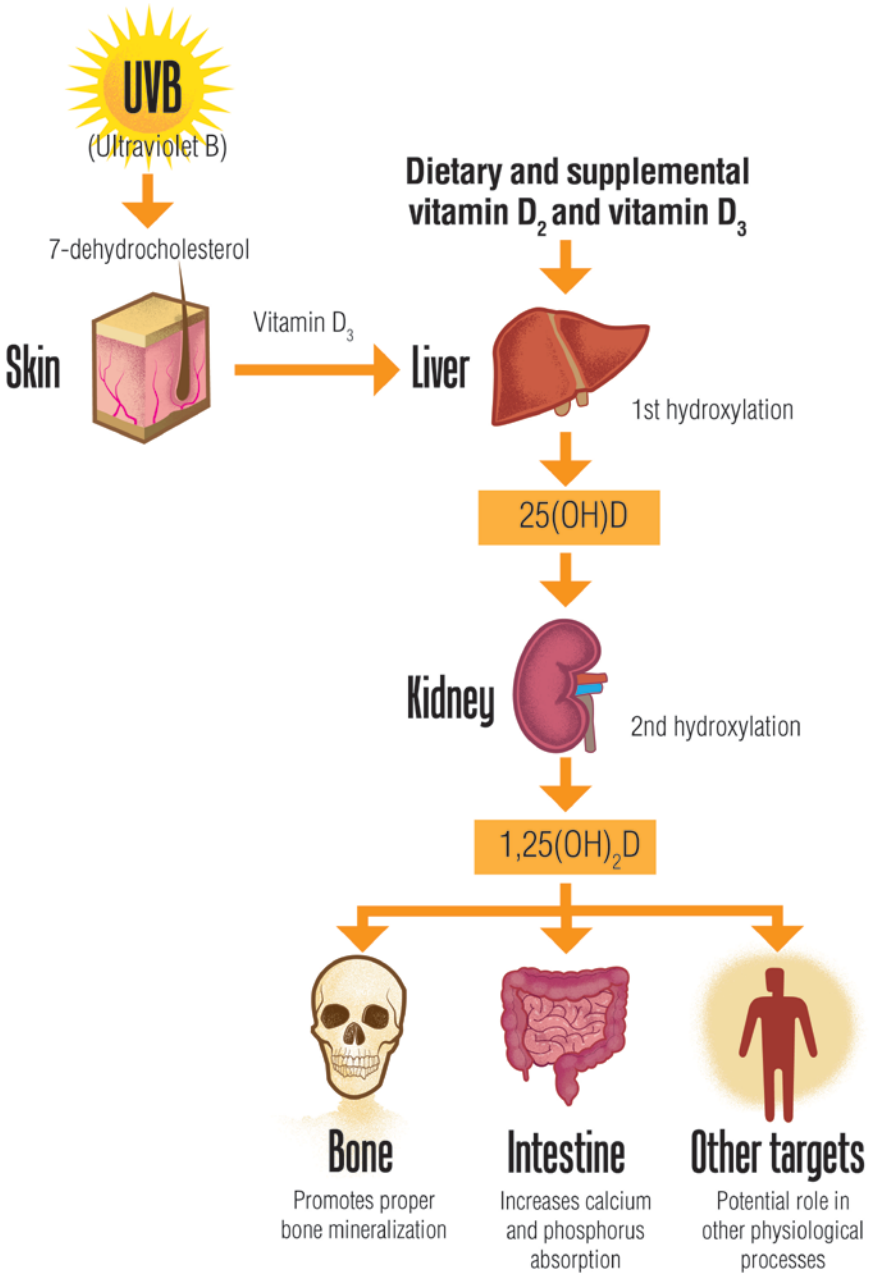


**Figure. Activation of Vitamin D.** Humans obtain vitamin D through endogenous production in the skin and through consumption of certain foods and dietary supplements. The form of vitamin D that originates from sun exposure, the diet, and supplements is biologically inert, and thus must undergo two hydroxylation steps before it can be utilized in physiologic processes. The first hydroxylation step occurs in the liver, where vitamin D is converted to 25-hydroxyvitamin D (25[OH]D), the main circulating and stored form of the vitamin. When vitamin D is required for physiological needs, like maintaining calcium and phosphorus homeostasis, 25(OH)D is hydroxylated, mainly in the kidneys, to its hormonally-active form 1,25-dihydroxyvitamin D ($1,25[OH]_2D$).

**Table 1. Serum 25-hydroxyvitamin D (25[OH]D) Concentration Cut Points and Associated Health Impact — Institute of Medicine, 2011**[7]

| Serum Level | | Health Impact in Healthy Persons |
|---|---|---|
| nmol/L | ng/mL | |
| <30 | <12 | Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults |
| 30 to <50 | 12 to <20 | Generally considered inadequate for bone and overall health in healthy individuals |
| ≥50 | ≥20 | Generally considered adequate for bone and overall health in healthy individuals |
| >125 | >50 | Emerging evidence links potential adverse effects to such high concentrations |

**Table 2. Dietary Reference Intake Components and their Corresponding Serum 25(OH)D Concentrations — Institute of Medicine, 2011**[7]

| Dietary Reference Intake (DRI) Components and Descriptions | | Corresponding serum 25(OH)D concentration |
|---|---|---|
| **Component** | **Description** | |
| **Adequate Intake (AI)** | Average intake level based on observed or experimentally determined estimates of nutrient intake by a group of people assumed to be maintaining adequate nutritional state. | 40–50 nmol/L |
| **Estimated Average Requirement (EAR)** | The estimated requirement to meet the nutrient needs of half the healthy individuals in a life-stage and age group in order to maintain adequate bone health and calcium metabolism. The EAR is used most often when determining adequate dietary intake amounts for groups of people (e.g., life-stage, age groups, and sex). | 52–59 nmol/L* |
| **Recommended Daily Allowance (RDA)** | Derived from the EAR, the RDA reflects an intake level that intends to meet the nutrient needs to maintain adequate bone health and calcium metabolism in 97.5% of the population. | 56–63 nmol/L* |
| **Tolerable Upper Intake Level (UL)** | The UL is the highest average daily intake that will likely pose no risk of adverse health effects to all individuals in the general population. As intake increases above the UL, the risk of adverse health effects may increase. | N/A |

**Corresponding 25(OH)D serum concentrations appear to overshoot the target level of 50 nmol/L because IOM adjusted for the fact that people respond differently to the same intake level.*[5]

**Table 3. Recommended Vitamin D Dietary Reference Intake Amounts, by Age–Group and Life–Stage — Institute of Medicine, 2011**[7]

| Life Stage/Age Group | | Dietary Reference Intake Component* | | | |
|---|---|---|---|---|---|
| | | **Adequate Intake (AI)** | **Estimated Average Requirement (EAR)** | **Recommended Daily Allowance (RDA)** | **Tolerable Upper Intake Level (UL)** |
| **Infants** | 0–6 mo | 400 IU (10 µg) | | | 1,000 IU (25 µg) |
| | 6–12 mo | 400 IU (10 µg) | | | 1,500 IU (38 µg) |
| **Children** | 1–3 years | | 400 IU (10 µg) | 600 IU (10 µg) | 2,500 IU (63 µg) |
| | 3–8 years | | 400 IU (10 µg) | 600 IU (10 µg) | 3,000 IU (75 µg) |
| **Males** | 9–70 years | | 400 IU (10 µg) | 600 IU (10 µg) | 4,000 IU (100 µg) |
| | >70 years | | 400 IU (10 µg) | 800 IU (10 µg) | 4,000 IU (100 µg) |
| **Females** | 9–70 years | | 400 IU (10 µg) | 600 IU (10 µg) | 4,000 IU (100 µg) |
| | >70 years | | 400 IU (10 µg) | 800 IU (10 µg) | 4,000 IU (100 µg) |
| **During Pregnancy or Lactation** (age 14–50 years) | | | 400 IU (10 µg) | 600 IU (10 µg) | 4,000 IU (100 µg) |

**IU=International Units*

**Table 4. Vitamin D Intake, Supplementation, and Screening Recommendations, by Professional and Governmental Body**

| Body | Population | Recommendation(s) |
|---|---|---|
| **US Preventative Services Task Force** 2009, 2014[21,34,35] | Adults (9–65 years) | **Intake/Supplementation:** In agreement with IOM DRIs<br><br>**Screening:** Do not recommend routine vitamin D screening in asymptomatic adults |
| | Adults (>65 years) | **Intake/Supplementation:** In agreement with IOM DRIs; supplementation should be considered for community-dwelling adults who are at increased risk for falls<br><br>**Screening:** Do not recommend routine vitamin D screening |
| **American Academy of Pediatrics** 2008[36,37] | Infants (0–12 months) | **Intake/Supplementation:** In agreement with IOM DRIs; recommend supplementation with 400 IU/day in all infants who are breastfed, mixed-fed (formula and breastmilk), and formula-fed that consume <1 L/day of formula |
| | Children (1–8 years) | **Intake/Supplementation:** In agreement with IOM DRIs<br><br>**Screening**: Advise screening for children and adolescents with reduced bone mass (e.g., anorexia, cystic fibrosis, chronic renal failure etc.) or those that experienced recurrent, low-impact fractures<br><br>Advise against routine screening for healthy children and even those considered to have certain risk factors for vitamin D deficiency (e.g., darker skin and obesity) because the evidence does not support benefits of screening in improving skeletal health in these demographics<br><br>The decision to screen and supplement should be on an individual basis between a pediatrician and their patients' family |
| **American Congress of Obstetricians and Gynecologists** 2011, reaffirmed in 2015[38] | Pregnancy and Lactation | **Intake/Supplementation:** In agreement with IOM DRIs; insufficient evidence for supplementation in pregnant women beyond the prenatal vitamin, which contains 400 IU/day vitamin D. Suggest that further recommendations should await completion of more RCTs<br><br>**Screening:** Advise screening in pregnant women thought to be at risk for deficiency; high-risk groups include vegetarians, limited sun exposure, and ethnic minorities |
| **American Geriatrics Society** 2014[39] | Adults (≥65 years) | **Intake/Supplementation:** Established 75 nmol/L to be the target serum 25(OH)D concentration, especially in those at higher risk for falls and fractures<br><br>Recommend additional supplementation of between 300–800 IU/day for individuals at risk for deficiency (e.g., darker skin, limited sun exposure, obesity)<br><br>Recommend 1,000 IU/day to reach and maintain 75 nmol/L |
| **National Osteoporosis Foundation** 2017[40] | Adults (≥9 years) | **Intake/ Supplementation:**<br>Recommend 400–800 IU daily for adults <50 years<br><br>Recommend 800–1000 IU for adults >50 years |

| Body | Population | Recommendation(s) |
|---|---|---|
| **Health Canada** 2012[41] | Infants (0–12 months) | **Intake/Supplementation:** In agreement with IOM DRIs; advise supplementation of 400 IU from birth through one year of age for infants who are breastfed |
| | Children (1–8 years) and Adults (≥9 years) | **Intake/Supplementation:** In agreement with IOM DRIs; advise supplementation of 400 IU for everyone aged >50 years |
| | Pregnancy and Lactation | **Intake/Supplementation:** In agreement with IOM DRIs |
| **U.S. Department of Defense** 2017[42] | Adults (≥9 years) | **Intake/Supplementation:** In agreement with IOM DRIs |