The Economics of Prevention

The financial implications of Alaska's vitamin D status

Representative Paul Seaton

Alaska State Legislature

House Finance Co-Chair

October 3, 2017

Alaska State Legislature

State Capitol Room 505
Juneau, Alaska 99801-1182
(907) 465-2689
1-800-665-2689

270 W. Pioneer Ave. Suite B
Homer, Alaska 99603
(907) 235-2921
Fax: (907) 235-4008
Kenai: (907) 283-9170

REPRESENTATIVE PAUL SEATON
Rep.Paul.Seaton@akleg.gov

October 3, 2017

To All Alaskans,

Today, our great state is facing historic financial challenges and decisions that will shape the state far into the future. Oil revenues, which have supported our state budget for so long, are no longer enough to cover the cost of services that Alaskans need and deserve. As co-chair of the House Finance Committee, my focus has been on restoring balance through the state budget both through revenue options and by looking for efficiencies and cost-saving options. With over 84,527 employees and retirees plus their dependents insured through the state and more than 93,000 insured through school districts and local government, and with Alaska healthcare spending increasing 31.8% since 2009, healthcare is a cost driver that cannot be ignored.

Prevention is key to reducing cost. Prevention comes in many forms, and one easy and cost effect option is maintaining a good health status through adequate vitamin D. Included in this book are three recent studies that look at the economics of prevention through vitamin D. The reports from Canada and Germany calculate the cost of poor health outcomes that could be avoided through adequate vitamin D; in Germany the authors calculated that the cost saving effect of national vitamin D sufficiency could be as much as €37.5 billion annually, more than €450 (over $530) per person. In his 2012 article in the Journal of Occupational and Environmental Medicine, Dr. Plotnikoff estimated that businesses could save an average of $370 per employee per year in lost productivity if the employees increased their vitamin D levels to greater than 40 ng.ml.

As the northern most state, Alaska is particularly at risk of vitamin D deficiency. Two Alaska public health bulletins indicate that vitamin D deficiency is a real and potentially growing concern for Alaskan children, particularly for Alaska Native children. Based on the economic analysis in the included studies, increasing vitamin D levels across Alaska could save hundreds of millions of healthcare dollars annually.

Sincerely,

Rep. Paul Seaton

State of Alaska May 20, 2014 Bulletin: Vitamin D Deficiency and Rickets among Alaska Native Children

Karrie Shelton, Alaska Division of Public Health: Dr. McLaughlin & Castrodale, Editors

Introductory Summary by Representative Paul Seaton

This 2014 bulletin compared rickets cases in Alaska Native Children, Alaska Native and American Indian Children living outside of Alaska, and the general US population over the years 2001-2010; an additional study compared Alaska Native rickets cases with healthy Alaska Native controls from 1999-2013. The results show that Alaska Native children are at an increased risk of vitamin D deficiency and rickets, and this risk appears to be increasing.

The average inpatient and outpatient rates of rickets for Alaska Native children during 2001-2010 was 6.7 per 100,000 (table 1), over four times the rate for Alaska Native/American Indian children outside the state and five and half times the rate for the general population. During the 1999 -2013 period the statewide average rate for Alaska Native children was 4.2 per 100,000. When broken out by region of residence, the incidence of rickets increased 2.3 fold for every 4° increase in latitude, indicating a strong correlation between northern latitudes and increased risk of vitamin D deficiency and rickets. Figure 1 of the bulletin shows the number of cases of Alaska Native rickets and vitamin D deficiency in the state, and it shows that this rate appears to be increasing over the last 10 years. Compared with healthy controls, more of the children with rickets were exclusively breastfed. Nearly half (48%) of the healthy controls received vitamin D supplements in their first 6 months of life, compared to only 17% of those children with diagnosed rickets or vitamin D deficiency.

This study highlights that Alaska Native children are at an increased risk of vitamin D deficiency and rickets, due in part to our northern latitude, and that all infants taking <1 liter of formula per day should receive vitamin D supplements.

Of note, this review of rickets cases did not compare rickets rates among the general Alaska pediatric population to the rest of the United States, perhaps due to insufficient available data. Given the correlation between latitude and risk shown by this case control study, it would be fair to assume that the general Alaska pediatric population is also at an increased risk as residents of the only arctic state.

State of Alaska November 1, 2016 Bulletin: Vitamin D Deficiency in Prenatal Alaska Native Women

Dr. Jay Butler, Alaska Division of Public Health: Dr. McLaughlin & Castrodale, Editors

Introductory Summary by Representative Paul Seaton

Alaska Native Children are at an increased risk of rickets due to low vitamin D levels, as shown by the previous 2014 bulletin. A high proportion of these rickets cases were in infants, indicating that the deficiency begins with the maternal vitamin D levels. This November 1, 2016 bulletin reviews three studies that examined prenatal and infant vitamin D levels in the Yukon-Kuskokwim Delta which found that woman of child bearing age (WCBA) and infants in the delta were almost universally vitamin D deficient or insufficient. Decreased vitamin D was associated with a reduction in traditional marine diets. Additional vitamin D supplementation and education was advised.

The first study tested blood samples from 1960 to 2015 for both vitamin D and a stable biomarker of marine food intake. The samples, from women aged 20-29 found that both vitamin D and marine food intake declined significantly from 1960 to 2000, supporting the theory that Alaska Native populations have become increasingly more at risk of vitamin D deficiency as they consume less of the traditional foods which are the best northern source of vitamin D.

The second and third studies tested maternal and infant cord blood vitamin D levels from 2001 – 2010 and in 2015. 28% of maternal samples from the first trimester were deficient (<20 ng/ml). At birth, *91% of cord blood samples were deficient* (<20 ng/ml) and 53% were severely deficient (<14 ng/ml). In 2015, 60% of mothers were deficient at delivery.

These studies show that as traditional diets have decreased, the risk of vitamin D deficiency and rickets in Alaska Native populations has significantly increased. An unacceptable 53% of infants were at a high risk of developing rickets and almost all YK Delta infants (91%) were vitamin D deficient. Given that the non-traditional diet these populations are transitioning to is the western diet consumed by the majority of Alaskans, it is a fair hypothesis to assume that non-native Alaskans are at a similar risk of vitamin D deficiency due to limited sun exposure and low dietary intake.

State of Alaska Epidemiology **Bulletin**

Department of Health and Social Services
William J. Streur, Commissioner
Ward B. Hurlburt, MD, MPH, CMO
3601 C Street, Suite 540
Anchorage, Alaska 99503 http://www.epi.Alaska.gov

Division of Public Health
Kerre Shelton, Director
Local (907) 269-8000
24 Hour Emergency (800) 478-0084

Editors:
Joe McLaughlin, MD, MPH
Louisa Castrodale, DVM, MPH

Bulletin No. 6 May 20, 2014

Vitamin D Deficiency and Rickets among Alaska Native Children

Background

Vitamin D comprises a group of fat-soluble secosteroids that are primarily responsible for maintaining normal serum concentrations of calcium and phosphate by increasing their absorption in the small intestine. Vitamin D deficiency leads to demineralization of bones and other tissues. Risk factors for vitamin D deficiency include living in northern latitudes, having darker pigmented skin, and being an exclusively breastfed infant.[1,2] Severe vitamin D deficiency in children can lead to bone deformities known as rickets. Likely due to reduced sun exposure and inadequate dietary vitamin D intake, the incidence of rickets appears to be increasing in developed countries and in Alaska.[1,3] The purpose of this study was to better understand the epidemiology of vitamin D deficiency and rickets among Alaska Native (AN) children.

Methods

We reviewed rickets and vitamin D deficiency cases among AN children aged <10 years. We calculated the incidence of rickets-associated visits (ICD-9-CM codes 268.0–.1) during 2001–2010 among children aged <10 years who were 1) AN, 2) American Indian/Alaska Native (AI/AN) from other Indian Health Service (IHS) regions, and 3) the general U.S. population. Cases were identified and rates calculated using the IHS Direct and Contract Inpatient and Outpatient Visit Database (IHSD) for AI/AN children,[4] and the Nationwide Inpatient Sample database for U.S. general child population.[5]

We also performed a case-control study to determine risk factors for vitamin D deficiency and rickets among AN children aged <10 years for cases identified from IHSD during 1999–2012, and from chart reviews. Nutritional vitamin D deficiency was defined as having a 25-OH-vitamin D level <15 ng/mL without rickets.[6] A nutritional rickets case was defined as clinical evidence of rickets confirmed by a pediatric endocrinologist. For each case, we identified and conducted chart reviews on 2–5 AN control participants, matched on birthdate and region.

Results

Rickets Rate Comparisons, United States and Alaska

During 2001–2010, the average annual inpatient and outpatient incidence of rickets among children aged <10 years was higher in AN children than in AI/AN children living in other IHS regions (Table 1). The inpatient incidence of rickets was also higher among AN children than for the general U.S. pediatric population (Table 1).

Table 1. Average Annual Rate of Rickets in Children Aged <10 Years — United States and Alaska, 2001–2010

Children Aged <10 Years	Inpatient Rate per 100,000	Outpatient Rate per 100,000
General U.S.	1.2 (95% CI 1.1–1.4)	N/A
Non-Alaska AI/AN	0.1	3.1
Alaska Native	2.2	11.2

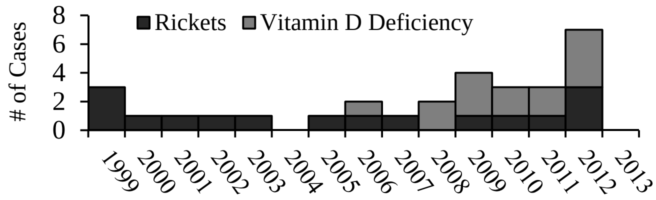
Rickets and Vitamin D Deficiency Cases in Alaska

During 1999–2012, 30 cases of nutritional rickets (n=16) and vitamin D deficiency (n=14) were identified among AN children aged <10 years (Figure); 18/30 (60%) were male. The mean age of diagnosis among rickets cases was younger than among children who had vitamin D deficiency without rickets (1.0 year vs. 4.0 years, respectively; p<0.01).

Children with rickets presented with the following clinical signs: 7/10 children who were diagnosed in their first 12 months of life presented with hypocalcemic seizures (n=3) or failure to thrive (n=4); 6/6 children who were diagnosed after 12 months of age presented with leg bowing. Radiographic findings in rickets patients included rachitic rosary, fractures, metaphyseal changes (in infants), and metaphyseal changes and leg bowing (in children aged >12 months).

During 1999–2013, the statewide average annual incidence of rickets among AN children aged <10 years was 4.2 per 100,000 persons. When examined by latitude of Alaska residence (between 50º and 73º), the incidence of rickets in this cohort of children increased 2.3 fold for every 4º increase in latitude (range 0–21.4 cases per 100,000 persons; p<0.001).

Figure. Cases of Rickets and Vitamin D Deficiency among AI/AN Children Aged <10 Years — Alaska, 1999–2012



Case-Control Study

Rickets and vitamin D deficiency cases were more likely than controls to have been diagnosed with malnutrition, and less likely than controls to have received vitamin D supplementation in the first 6 months of life (Table 2).

Table 2. Comparison of Rickets or Vitamin D Deficiency Cases with Matched Controls — Alaska, 1999–2013

	Cases N=26 (%)	Controls N=93 (%)	Matched OR (p-value)
Male sex	14 (54)	39 (42)	1.7 (0.25)
Malnutrition	12 (47)	2 (2)	**38.1 (0.001)**
Exclusively formula-fed	2/20 (10)	13/79 (16)	0.31 (0.28)
Ever solely breast fed	10/15 (67)	39/75 (52)	2.1 (0.29)
Vitamin D Supplement*	3/18 (17)	32/67 (48)	**0.2 (0.03)**

***Vitamin D supplementation at some point during the first 6 months of life among infants diagnosed with rickets at ≥6 months of age.*

Discussion

Rickets was more common in AN children than in other U.S. children, and the incidence of rickets increased with increasing geographic latitude within Alaska. Providers should be aware that vitamin D deficiency remains a concern for children living in Alaska. This study highlights the importance of recognizing the following pediatric risk factors for rickets in Alaska: general malnutrition, darker pigmentation, living at higher latitude, and lack of vitamin D supplementation in breastfed and formula fed infants. Health care providers should consider vitamin D screening of high-risk children and those with signs or symptoms of rickets. All infants taking <1L of formula should receive 400 IU of vitamin D daily.[2]

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(Contributed by: Rosalyn Singleton MD, ANTHC, Rachel Lescher MD, ANTHC, Matthew Benson MD, ANTHC, Bradford Gessner MD, Lisa Bulkow MS, CDC-AIP, John Rosenfeld MD, ANTHC, James Tiesinga, MD, ANTHC, Michael Bruce MD, CDC-AIP)

State of Alaska Epidemiology **Bulletin**

Department of Health and Social Services
Valerie J. Davidson, Commissioner

3601 C Street, Suite 540
Anchorage, Alaska 99503 http://dhss.alaska.gov/dph/Epi

Division of Public Health
Jay C. Butler, MD, Chief Medical Officer and Director

Local (907) 269-8000
24 Hour Emergency (800) 478-0084

Editors:
Joe McLaughlin, MD, MPH
Louisa Castrodale, DVM, MPH

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Vitamin D Deficiency in Prenatal Alaska Native Women

Background

Rickets is more common in Alaska Native (AN) children than in other U.S. children, with an average annual incidence of 4.2 cases per 100,000 children aged <10 years.[1] Of 16 confirmed AN rickets cases during 1999–2013, 10 (63%) were in infants, underscoring the importance of maternal vitamin D status.[1] Previous dietary evaluations have shown that traditional AN subsistence diets are rich in vitamin D.[1]

This *Bulletin* presents results from three studies that examined the prevalence of vitamin D deficiency in AN women of childbearing age (WCBA) in one Alaska region. The first study explored the role that changing diets in WCBA might have on infant vitamin D deficiency by measuring trends in traditional marine food intake and serum vitamin D levels in Southwest AN WCBA from the 1960s to the present.[2] Next, the Maternal Organic Monitoring (MOM) Study attempted to verify the results of the aforementioned study with recent data. Lastly, YK Delta Regional Hospital (YKDRH) evaluated serum vitamin D concentrations of pregnant women at the time of delivery over a 3-month period during the fall of 2015.

Methods/Results

For all three studies, vitamin D deficiency was defined as a serum concentration of 25(OH)D <20 ng/mL or <50 nmol/).[3]

Study 1. Concentrations of 25-hydroxycholecalciferol (25(OH)D_3) and a stable isotope biomarker of traditional marine food intake, the $\delta^{15}N$ value, were measured in 100 serum samples archived in the Alaska Area Specimen Bank and in current samples. The samples were obtained during 1960–2015 from women aged 20–29 years living in the YK Delta (YKD) region. Sample results were analyzed for trends.[3]

Intake of a traditional marine diet as measured by serum $\delta^{15}N$ values decreased significantly during 1960–1999 ($p<0.0001$), then remained stable during 2000–2015 (Figure 1A).[2] Serum 25(OH)D_3 concentrations also decreased significantly from the 1960s to the present ($p<0.0001$, Figure 1B). Serum $\delta^{15}N$ values were highly correlated with 25(OH)D_3 concentrations ($p<0.0001$).[3]

Study 2. During 2001–2010, blood was collected from pregnant AN women living in the Southwest region at enrollment in the first trimester, and cord blood was collected at delivery; serum 25(OH)D was measured in maternal and cord blood.[4]

In this study, 28% (45/159) of maternal blood samples drawn at prenatal visits and 91% (71/78) of cord blood samples had 25(OH)D concentrations <50 nmol/L; 53% (41/78) of cord bloods had 25(OH)D concentrations <35 nmol/L (indicating severe vitamin D deficiency).[4]

Study 3. In response to the two previous studies, YKDRH measured 25(OH)D levels on approximately 25% of pregnant mothers at prenatal visits and delivery during the fall of 2015 (on average, roughly 150 women deliver at YKDRH during a 3-month period).

During the 2015 YKDRH evaluation of vitamin D in prenatal women, 60% (24/40) were vitamin D deficient at delivery.

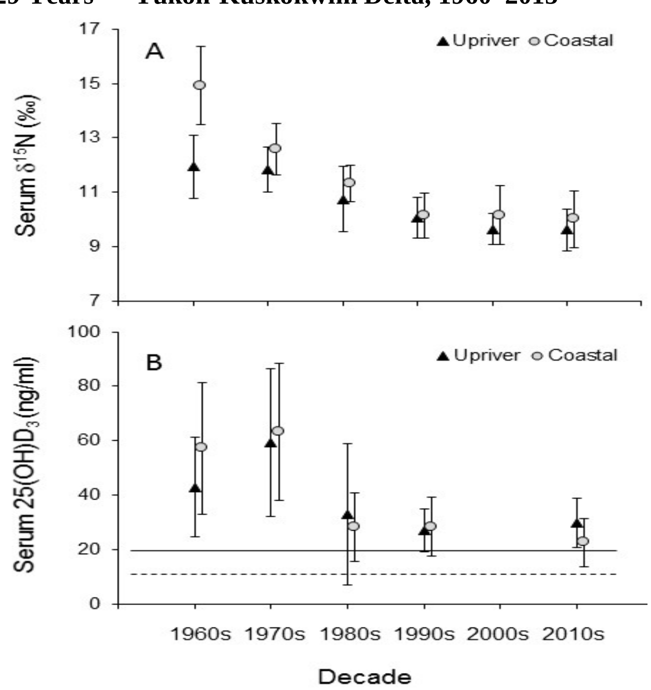
Discussion

In Alaska, consumption of traditional marine foods by young AN women in the Southwest region dropped significantly during the 1960s through the 1990s concurrent with a significant decline in vitamin D levels. Cord blood vitamin D levels in AN infants living in the Southwest region were uniformly low in the MOM study (2001–2010). In 2015, over half of YKD women tested during a prenatal vitamin D evaluation were vitamin D deficient at delivery. Data from these three studies suggest that vitamin D deficiency appears to be highly prevalent in YKD prenatal women. While current evidence does not support routine vitamin D screening and supplementation for prenatal women on a national level,[5,6] such screening and supplementation appears to be warranted in YKD. More research is needed to better understand the epidemiology of vitamin D deficiency in YKD and other Alaska regions.

Current Interventions

1. YKDRH consulted with vitamin D experts and developed guidelines to supplement routinely recommended prenatal vitamins (400 IU/day)[6] with an additional 1000 IU of daily vitamin D and to monitor prenatal vitamin D levels.
2. The Alaska Native Medical Center (ANMC) changed from infant Trivisol (containing vitamins A, D, and C) to one drop of “Baby D drops” to improve adherence.
3. Programs are in place to promote traditional food consumption among AN, such as ANMC’s “Store Outside Your Door” and the Center for AN Health Research’s “Fish to Schools”.
4. The Alaska Native Tribal Health Consortium (ANTHC) developed a research proposal to introduce Native foods into Head Start lunch programs.
5. ANTHC and YK Health Corporation are conducting an analysis of the relationship between prenatal vitamin D levels and early childhood caries. Other outcomes of interest include preterm birth, birthweight, gestational diabetes, and pre-eclampsia.

Figure 1. Differences in Mean (A) Serum $\delta^{15}N$ Values, and (B) Serum 25(OH)D_3 Concentrations in Women Aged 20–29 Years — Yukon-Kuskokwim Delta, 1960–2015[2]



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(Contributed by: Rosalyn Singleton MD, Rachel Lescher MD, James Berner MD, Alaska Native Tribal Health Consortium; Lisa Bulkow MS, CDC-Arctic Investigation Program; Diane O’Brien PhD, U. Alaska Fairbanks; Ken Thummel, PhD, U. Washington; Joseph Klejka MD, Yukon Kuskokwim Health Corporation.)

Estimated Economic Benefit of Increasing 25-hydroxyvitamin D Concentrations of Canadians to or above 100 nmol/L (40 ng/ml)

Grant et al., Dermato-Endocrinology

Introductory Summary by Representative Paul Seaton

As one of the largest and steadily increasing cost drivers in the budget, the economics of healthcare are of particular importance to the House Finance Committee. Controlling the rise in healthcare costs will help to stabilize the budget and put us on a path to sustainability. This review by Dr. Grant examines how the prevention of disease through adequate vitamin D levels could save Canada billions of dollars annually. With a national population of 36.3 million and potential annual cost savings of $12.5 billion, that equates to $344 saved per person per year. As our nearest neighbor Canada is geographically and demographically similar to Alaska. However since the per person cost of health care in Alaska is approximately twice that of Canada, the simple preventive step of raising Alaskan vitamin D levels could lead to as much as $688 in per person savings. As Dr. Grant notes, it is important to recognize that these healthcare cost savings will not be instantaneous; the benefits of prevention accrue over time as the incidence of new health problems is reduced.

In this 2016 study, Dr. Grant and associates used observational studies and recent data on 25-hydroxyvitamin D concentrations of Canadians from the Canadian Health Measures Survey to estimate the potential reduction in disease incidence, mortality rates, and the total direct and indirect economic burden of disease if vitamin D concentrations of all Canadians were raised to or above 40 ng/ml (100 nmol/L)[i]. The analysis found that increasing vitamin D levels could prevent an estimated 23,000 premature deaths and save Canada $12.5 billion in healthcare spending and costs annually, though the authors noted that the savings would take several years to reach the estimated level because they are based on *prevention* of disease and not the treatment of already established chronic diseases. Estimates were primarily based on observational studies due to a current lack of well-designed clinical trials.

The vitamin D levels of Canadians have declined since a similar analysis was performed in 2010; the mean level has dropped from 26.8 ng/ml in 2010 to 24.4 ng/ml. 6.9%-13.2% of Canadians, depending on whether it was summer or winter, were severely deficient in vitamin D (<12 ng/ml). 35% of all Canadians did not even meet the Health Canada guideline levels of at least 20 ng/ml. The authors noted that even though the intent was to analyze the savings if the mean Canadian vitamin D level was raised to 40 ng/ml, there would also be benefits of all Canadians reaching levels of >20 ng/ml. The literature indicates that 40 ng/ml is the blood level where the risk reduction is most significant for the widest range of diseases. Observational studies and clinical trials both indicate that the greatest benefit of increasing their vitamin D status would be to the 35% of Canadians who currently have levels below 20 ng/ml. To raise vitamin D levels, the authors recommend that Canadians would have to take 1000-4000 IU per day, depending on the target level, or spend adequate time in the sun. Supplements were high recommended as the average Canadian can only obtain 200-300 IU/d from food alone. Many Canadians do not have optimal vitamin D levels as a result of limited solar exposure, and increasing their vitamin D status could result in significant healthcare savings through reduced disease incidence.

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[i] This article uses nmol/L to measure vitamin D status, whereas ng/ml is the more common unit in the United States. The conversion factor for ng/ml to nmol/L is 2.5; multiple the ng/ml value by 2.5 to get the estimated nmol/L value or divide the nmol/L value by 2.5 to determine the ng/ml value. For clarity, the nmol/L values of the article have been converted to ng/ml for this summary introduction.

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REVIEW

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Estimated economic benefit of increasing 25-hydroxyvitamin D concentrations of Canadians to or above 100 nmol/L

William B. Grant [a], Susan J. Whiting [b], Gerry K. Schwalfenberg [c], Stephen J. Genuis [d], and Samantha M. Kimball[e]

[a]Sunlight, Nutrition, and Health Research Center, San Francisco, CA, USA; [b]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada; [c]Department of Family Medicine, University of Alberta, Edmonton, Alberta, Canada; [d]Faculty of Medicine at the University of Alberta, Edmonton, Alberta, Canada; [e]Pure North S'Energy Foundation, Calgary, Alberta, Canada

ABSTRACT

Mounting evidence from observational and clinical trials indicates that optimal vitamin D reduces the risk of many diseases. We used observational studies and recent data on 25-hydroxyvitamin D [25(OH)D] concentrations of Canadians from Cycle 3 of the Canadian Health Measures Survey to estimate the reduction in disease incidence, mortality rates, and the total economic burden (direct plus indirect) of disease if 25(OH)D concentrations of all Canadians were raised to or above 100 nmol/L. Recently, the mean 25(OH)D concentration of Canadians varied depending on age and season (51–69 nmol/L), with an overall mean of 61 nmol/L. The diseases affected by 25(OH)D concentration included cancer, cardiovascular disease, dementia, diabetes mellitus, multiple sclerosis, respiratory infections, and musculoskeletal disorders. We used 25(OH)D concentration–health outcome relations for breast cancer and cardiovascular disease and results of clinical trials with vitamin D for respiratory infections and musculoskeletal disorders to estimate the reductions in disease burden for increased 25(OH)D concentrations. If all Canadians attained 25(OH)D concentrations > 100 nmol/L, the calculated reduction in annual economic burden of disease was \$12.5 ± 6 billion on the basis of economic burdens for 2016 and a reduction in annual premature deaths by 23,000 (11,000–34,000) on the basis of rates for 2011. However, the effects on disease incidence, economic burden, and mortality rate would be phased in gradually over several years primarily because once a chronic disease is established, vitamin D affects its progression only modestly. Nevertheless, national policy changes are justified to improve vitamin D status of Canadians through promotion of safe sun exposure messages, vitamin D supplement use, and/or facilitation of food fortification.

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Introduction

During the past 15 years, considerable interest in the health benefits of vitamin D has emerged because people with higher ultraviolet-B (UVB) exposure and/or 25-hydroxyvitamin D [25(OH)D] concentrations have lower risk of many diseases and conditions.[1] Our analysis is limited to the diseases with the greatest economic effect and the strongest evidence of protective roles of vitamin D—namely, cancer, cardiovascular disease (CVD), dementia, diabetes mellitus (DM), falls and fractures, multiple sclerosis (MS), and respiratory tract infections.

Table 1 outlines information supporting the role of vitamin D in reducing risk of those diseases. The papers cited regarding mechanisms are given to indicate that the findings from observational studies and clinical trials are very likely to be causal rather than coincidental. The observational studies listed are the ones used to determine 25(OH)D concentration–health outcome relations. The clinical trials listed further support the role of vitamin D for some diseases. Observational studies rather than clinical trials provide much of the information on which to base the analyses that follow. Few well-designed clinical trials show beneficial effects of vitamin D mainly because many such trials were based on guidelines for pharmaceutical drugs. Two basic assumptions underlie such trials: that the trial is the only source of the agent and that a linear dose–response relation exists. Neither assumption holds for vitamin D. Robert Heaney

CONTACT William B. Grant wbgrant@infionline.net Sunlight, Nutrition, and Health Research Center, P.O. Box 641603, San Francisco, CA 94164-1603, USA.

Table 1. Diseases included in this study along with a brief overview of the mechanisms of vitamin D for each disease and a listing of a few observational studies and clinical trials in support.

Disease	Mechanisms	Observational studies	Clinical trials
Cancer	Effects on cells, angiogenesis, and metastasis[10]	Breast and colorectal cancer incidence[11]; survival[12]	Breast and all-cancer incidence[13]
CVD	Effects on serum cholesterol levels, arterial stiffness, insulin resistance, hyperglycemia, and increased incident metabolic syndrome are potentially plausible mediators[8]	Refs.[14,15]	Effect on CVD risk factors[16]
Dementia	Regulation of calcium homeostasis, clearance of amyloid-β peptide, antioxidant and anti-inflammatory effects, and possible protection against the neurodegenerative mechanisms associated with AD[17]	Incidence[18]	
DM	Improves insulin sensitivity and secretion, mainly via its anti-inflammatory properties[19]	Incidence[20]; meta-analysis[21]	
Falls and fractures	Reduces bone mass loss by reducing inflammation[22]; maintains cognition[23]; helps maintain muscle mass[24]	Ref.[25]	Ref.[26]
MS	Effects on regulatory T and B cells[27]	Ref.[28]	
Respiratory infections	Induction of cathelicidin and defensins[29]; strengthens adaptive and innate immune system[30]	Pneumonia[31]	Influenza[32,33]; ARI[34]

AD, Alzheimer disease; ARI, acute respiratory tract infection; CVD, cardiovascular disease; DM, diabetes mellitus; MS, multiple sclerosis.

outlined the guidelines for nutrient studies including vitamin D. The most relevant features are that one should start with an understanding of the 25(OH)D concentration–health outcome relation, 25(OH)D concentrations should be measured in prospective participants, only those with low concentrations should be enrolled, sufficient vitamin D should be given to raise 25(OH)D concentrations to where a significant beneficial effect is expected, and achieved 25(OH)D concentrations should be measured.[2] Until those steps are followed routinely, few vitamin D clinical trials will report beneficial effects. A review of clinical trials of vitamin D with respect to biomarkers of inflammation shows why following those guidelines is important. For trials that had baseline concentrations below 49 nmol/L, 50% of the trials found a beneficial effect, but for trials with higher baseline concentrations, only 26% did.[3] That observational studies can be used in the interim can be justified in several ways. For one, the effects of other nutrients have been established based on observational and laboratory studies, such as the risk of cancer from eating meat.[4] For another, Hill's criteria for causality in a biological system can be used to evaluate the findings from a large diversity of studies. The criteria most relevant for vitamin D are strength of association, consistent findings in different populations, temporality, biological gradient, plausibility (e.g., mechanisms), coherence with known facts, and experiments (e.g., clinical trials).[5] Not all criteria need be satisfied, but the more that are, the stronger the case. Hill's criteria have been used to evaluate the beneficial effects of vitamin D for cancer,[6,7] CVD,[8] and MS.[9]

The purpose of this new study is to revisit vitamin D concentrations of Canadians and to estimate the economic benefit of increasing 25(OH)D concentrations, with the knowledge that overall 25(OH)D concentrations have gone down since our previous study. The evidence for the role of vitamin D for diseases considered in 2010 has increased. Many additional published studies have shown that optimal 25(OH)D concentrations are required to prevent many more chronic as well as acute conditions. As a result, the estimates of the economic burden of disease may have changed.

Materials and methods

Publications on the relations between 25(OH)D concentrations and health outcomes were obtained largely by searching pubmed.gov and scholar.google.com for terms such as *vitamin D, 25-hydroxyvitamin D, meta-analysis, back and spine disorders, cancer, cardiovascular disease, immune system, osteoporosis, respiratory infection, economic burden, Canada, cost, season, mortality, incidence*, and *risk*. Data on the economic burdens of diseases in Canada were found by searching those sites as well as using Google. The definition of *economic burden* used here includes both direct medical treatment costs and indirect costs such as time lost from work and premature death.

25-Hydroxyvitamin D concentrations

Previously unpublished data on 25(OH)D concentrations for Canadians measured from the Canadian Health Measures Survey (CHMS) Cycle 3 (conducted throughout 2012 and 2013)[35] were obtained from the Health Statistics Branch of Statistics Canada, Ottawa, Canada. The overall response rate for cycle 3 was 51.7%, yielding 5,785 respondents aged 3–79 y who completed the household questionnaire and mobile examination center visit. Detailed information on the collection and measurement of plasma 25(OH)D in the CHMS can be found in the Vitamin D Reference Laboratory Standard Operating Procedures Manual at www.statcan.gc.ca. The assay was conducted by chemiluminescence immunoassay on the Diasorin Liaison autoimmunoanalyzer (Stillwater, MN). The CHMS survey targets the following precision estimates: 20 nmol/L = 15%; 20–100 nmol/L = 10%; > 100 nmol/L = 12%.

New data from the 2012–2013 Canadian Health Measures Survey obtained from Statistics Canada demonstrate the most recent 25(OH)D measured for Canadians. Mean 25(OH)D concentrations varied slightly by age group: 62.3 nmol/L (95% confidence interval [CI], 55.6–68.9 nmol/L) for those aged 3–19 years; 57.2 nmol/L (95% CI, 50.2–64.3 nmol/L) for those aged 20–49 years; and 66.3 nmol/L (95% CI, 60.9–71.8 nmol/L) for those aged 50–79 y. Concentrations measured in summers were approximately 10 nmol/L higher than in winter, except for the oldest group (age 50–79 y), where only a 6-nmol/L difference was seen between seasons. As far as the prevalence of severe deficiency (< 30 nmol/L), 6.9% of Canadians were in that category in summer, and that figure doubled to 13.2% with severe deficiency in winter. Similarly, a seasonal effect in prevalence of deficiency (i.e., concentrations between 30 and 49.9 nmol/L) was seen, where Canadians in winter had a 50% higher prevalence of deficiency than in summer. Only a small percentage of Canadians, 7.8% in summer and 3.8% in winter, had 25(OH)D concentrations at or above 100 nmol/L, and very few (below the threshold allowable for publishing) were in the range of 125 nmol/L and above.

Table 2. Estimated cumulative percentage of Canadians aged 50–79 y with 25(OH)D concentrations in the various range groups.

25(OH)D group (nmol/L)	25(OH)D max	Summer cumulative percentage	Winter cumulative percentage
<30	30.0	6.0	
30–49.9	49.9	26.0	
50–62.4	62.4	46.7	
	68.7	50.0	
62.5–74.9	74.9	70.1	
75–99.9	99.9	89.9	
>100	105.0	100.9	
<30	30.0		11.2
30–49.9	49.9		38.9
50–62.4	62.4		59.9
62.6			50.0
62.5–74.9	74.9		76.3
75–99.9	99.9		97.7
>100	105.0		100.0

The data of those aged 20–49 y and 50–79 y were used to estimate the cumulative percentage with 25 (OH)D concentrations as a function of 25(OH)D concentration. The values for summer and winter were plotted together and were fit with a linear function. The values obtained are given in Table 2. Those values were used to estimate the mean 25(OH)D concentration for each 25(OH)D concentration decile.

We derived the estimated reduction in economic burden by using the Cycle 3 distribution of 25(OH)D in increments of 10 nmol/L. To determine the effect of increasing 25(OH)D concentration to above 100 nmol/L, the appropriate 25(OH)D concentration percentile values were convolved with the 25(OH)D concentration–health outcome relation for each disease by using recently published estimates. If a single observational study was used, the odds ratio or hazard ratio value was used for 25(OH)D concentrations 5, 15, 25, … 95 nmol/L.[36]

The sum of the population percentage multiplied by the relative risk at each 25(OH)D decile is divided by the sum of the percentages of the population and by the relative risk for the 10th decile, which gives the factor higher for the present 25(OH)D concentration distribution than if all had >100 nmol/L; that is, 36.5/95.0/0.13 = 2.96. The reciprocal of that value gives the estimate of the incidence rate after increasing 25(OH) D concentrations: 1/2.96 = 0.34, or a 66% reduction in that example in incidence of MS.

Data for the economic burden of disease were obtained from various publications. Usually, the available data were for a year 5–10 y before 2016. To convert those values to 2016 values, we adjusted for both inflation and population changes. The equation used is

$$\text{Burden}_{2016} = \text{Burden}_{\text{year}} \times 1.025^{(2016 - \text{year})}$$

According to the Canadian Institute for Health Information, per capita annual growth rates for total health expenditures increased by 3.3% per year from the late 1990s to 2010 and by 0.6% from 2011 to 2015.[37] The consumer price index increased from 97.8 in 2001 to 126.6 in 2015.[38] That finding corresponds to a 2%/yr increase. Those rates are used to calculate economic burden estimates for 2016.

Details of calculations for health outcomes

Cardiovascular disease

CVD includes several related diseases such as coronary heart disease, acute myocardial infarction, congestive heart failure, cerebrovascular disease (stroke), and peripheral arterial disease. CVD accounted for the second-largest portion of deaths in Canada in 2011, with 47,627 deaths from heart disease and 13,283 deaths from stroke annually (total, 60,910).[39] Total cost for CVD in Canada was estimated at $20.9 billion in 2005 (in constant 2008 Canadian dollars) and was expected to rise to $28.3 billion in 2020.[40] The costs increased at 2%/yr. Thus, in 2016, the cost would be $24.6 billion.

The 25(OH)D concentration–CVD relation in Ref. (15) is the starting point for the calculations. That relation was based on 19 independent prospective studies that included 6 related to CVD incidence. Risk of CVD is an estimated 24% higher for those aged 30–49 y than would be the case if everyone had 25 (OH)D concentrations >75 nmol/L, whereas it is 16% higher for those aged 50–79 y (Table 3). Based on the percentage of the Canadian population with CVD in 2009[41] and the population distribution in Canada in 2014,[42] the distribution of CVD in Canada is 11% for those aged 20–49 y and 89% for people older than 50 y. Thus, the reduction in CVD is expected to be $0.11 \times (1/1.24) + 0.89 \times (1/1.16) = 0.86$, or a 14% reduction.

Cancer

An estimated 196,900 new cases of cancer and 78,000 deaths from cancer will occur in Canada in 2015.[43]

The total economic effect of cancer in 2010 was $6.5 billion,[44] of which direct medical costs make up more than half. After adjustment for increase in total population increase and inflation, the total economic burden in 2016 is estimated at

$$\$6.5\ \text{billion} \times (36.3\ \text{million}/34.0\ \text{million}) \times [0.5 \times (1.02)^6 + 0.5 \times (0.994)^6] = \$7.3\ \text{billion}$$

The evidence is considered strongest for colorectal cancer since most prospective studies reported significant inverse correlations between 25(OH)D concentration at time of enrollment and incidence of colorectal cancer, with relative risk of about 0.4 for highest versus lowest 25(OH)D concentration for short follow-up times.[11] Breast cancer incidence rates have a risk of about 0.55 for high vs. low 25(OH)D concentration and short follow-up times.[11] Pancreatic cancer incidence inversely correlated with 25(OH)D concentration in a pooled analysis from 5 cohort studies.[45] For lung cancer, a study in Denmark found a 20% increased risk of lung cancer for a 50% reduction in 25(OH)D concentration.[46] Lung cancer risk is inversely correlated with 25(OH)D concentration, with risk at 50 nmol/L being 88% of that at 20 nmol/L according to a meta-analysis of observational studies.[47]

The 25(OH)D concentration–breast cancer incidence relation based on case–control studies is shown in Figure 2 in Ref. 11. Using the values in that graph with the mean values for each decile of 25(OH)D concentration for those aged 50–79 y yields an odds ratio of 1.60 compared with the case in which all had 25(OH)D concentrations >100 nmol/L (Table 4). Thus, breast cancer incidence rates would be expected to be reduced by 40% if everyone had 25(OH)D concentrations>100 nmol/L.

To use the 25(OH)D concentration–breast cancer incidence relation for all-cancer incidence, comparisons have to be made with all-cancer incidence and/or mortality rates from various studies. In a clinical trial, taking 400 IU/d of vitamin D_3plus1500 mg/d of calcium reduced breast, invasive breast, and all-cancer incidence by 14%–20% for women who were not taking those supplements before entering the study.[13] That finding is consistent with the 25(OH)D concentration–breast cancer incidence relation in Ref. 11. In the US for 1970–1994, the contribution from smoking and diet was slightly larger than UVB dose for all less lung cancer mortality rate for males, whereas for women, the contribution from smoking and diet was about half that for UVB.[48] In Nordic countries, smoking and UVB exposure contributed nearly equally to cancer risk for males.[49] Data from that study were not reliable for females.

A meta-analysis of lung cancer incidence versus 25(OH)D concentration at the time of enrollment found that relative risk decreased from 1.0 at 20 nmol/L to 0.86 at 40 nmol/L and 0.84 at 50 nmol/L, after which the 95% confidence intervals became very large.[47] Most of the 13 studies were prospective studies with long follow-up times, and one study involved smokers who had taken large doses of vitamin A, which may have affected cancer risk since it competes with vitamin D.[50] Thus, doubling the calculated change in relative risk to 0.72 at 40 nmol/L and 0.68 at 50 nmol/L and higher seems reasonable.

Rising rates of obesity also affect cancer rates. The International Agency for Research on Cancer has adjudicated excess body fat as an important risk factor for 13 cancers.[51] The rapid rise in obesity rates in the US may help explain why correlations between solar UVB dose and breast cancer mortality rates have decreased significantly from 1950–1954 to 2000–2004 in addition to the fact that people spend less time in the sun and cover up more with clothing and sunscreen when in the sun.[52]

With the information in the preceding paragraphs taken together, assuming the 25(OH)D concentration–all cancer incidence relation to be 40% of that of breast cancer seems reasonable. Thus, the estimated reduction in cancer risk is estimated at 6% if people with 25(OH)D concentrations <50 nmol/L were raised to >50 nmol/L, 10% if people with 25(OH)D concentration <75 nmol/L were raised to >75 nmol/L, and 15% if all were raised to >100 nmol/L.

Based on data from the US for 2004–2013, using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, cancer incidence rates for those aged 20–49 y is 2% of that for those aged >50 y.[53]

Respiratory infections

Influenza and pneumonia accounted for 5,694 deaths of Canadians in 2012.[54] The total economic impact for respiratory infections was \$5.4 billion in 2008.[55] The estimated economic burden in 2016 is

$$\$5.4 \text{ billion} \times (1.033)^2 \times (0.994)^6 \times (36.3 \text{ million}/33.3 \text{ million}) = \$6.1 \text{ billion}$$

Clinical trials support the role of vitamin D in reducing risk of influenza. A clinical trial involving black postmenopausal women living on Long Island, New York, found that only one of those taking 2000 IU/d of vitamin D_3 developed a cold or influenza, compared with 8 taking 800 IU/d and 30 taking a placebo.[32] There were 312 person-years of placebo, 208 person-years of 800 IU/d, and 104 person-years of 2000 IU/d. Baseline 25(OH)D concentration was 47 ± 21 nmol/L. In a later clinical trial involving mostly white Americans by the same group, the baseline 25(OH)D concentration was 64 ± 25 nmol/L, vitamin D_3 supplementation was 2000 IU/d, and the achieved 25(OH)D concentration was 89 ± 23 nmol/L.[56] That study did not find a beneficial effect on upper respiratory tract infections in winter in comparison with the placebo arm. A clinical trial involving 8- to 12-year-old schoolchildren in Japan receiving 1200 IU/d of vitamin D_3 found a significant reduction in incidence of type A influenza for those who had not been taking vitamin D supplements (relative risk = 0.36 [95% CI, 0.17–0.79]).[33] A study in Mongolia involving children near 10 y of age with a baseline 25(OH)D concentration of 18 nmol/L (95% CI, 13–25 nmol/L) found that giving them a loading dose of vitamin D_3 followed by 300 IU/d of vitamin D, which raised the 25(OH)D concentration to 47 nmol/L (95% CI, 39–57 nmol/L), resulted in a 3-month adjusted relative risk of acute respiratory tract infections (ARIs) of 0.50 (95% CI, 0.28–0.88).[34] That study shows that people with low 25(OH)D concentrations have significant reductions in ARIs with modest increases in 25(OH)D concentrations.

Results of observational studies can be used to estimate the reduction in respiratory tract infections. Two prospective studies on incidence of pneumonia among the elderly yielded information on the 25(OH)D concentration–pneumonia incidence relation—one from Finland,[57] one from the US[31] Using those values along with the 25(OH)D concentration percentiles for elderly Canadians results in a 31% reduction in pneumonia on the basis of the Finnish study and a 72% reduction on the basis of the US study. Closer to home is a study from Canada based on students at McMaster University, Hamilton, Ontario, that enrolled 600 students. A comparison during September–October found a relative risk of clinical upper respiratory tract infection of 0.79 (95% CI, 0.61–1.03; $p = 0.09$) for 258 students taking 10,000 IU/wk of vitamin D_3, compared with 234 students taking a placebo.[58] Although that study did not measure 25(OH)D concentrations, it indicates that young Canadians taking the equivalent of 1400 IU/d of vitamin D had a marginally nonsignificantly reduced risk of upper respiratory tract infections. On the basis of findings from clinical trials and observational studies, a reduction of 25% is considered reasonable if all Canadians had 25(OH)D concentrations greater than 100 nmol/L. That change could translate to a reduction of 1400 deaths/yr and $1.5 billion in total costs.

Diabetes mellitus

DM affects more than3 million Canadians and is responsible for an economic burden of $15.4 billion in 2015[59] ($15.7 billion in 2016, assuming 2.5%/yr general inflation and −0.6% health cost inflation) and 3% of Canadian deaths per year.

Observational studies offer good evidence that vitamin D affects risk of DM. A meta-analysis of incidence of DM type 2 with respect to 25(OH)D concentration based on 18 prospective studies found a relative risk of 0.5 for 25(OH)D concentration of 155 nmol/L, compared with 35 nmol/L.[21] However, few data at high 25(OH)D concentrations were available. To analyze reduced risk of DM, we used the values of the regression analysis by Song and colleagues for 80 nmol/L as the lowest relative risk. That gives an estimate of DM incidence 23% higher for those aged 20–49 y and 20% higher for those aged 50–79 y. From incidence data in Ref. 60 along with the age distribution of the population,[42] one-third of diabetes is diagnosed before 50 y of age and 2-thirds after 50 y (Table 5). Thus, raising 25(OH)D concentrations of all Canadians to >80 nmol/L could reduce risk of DM to $0.33\times(1/1.23) + 0.67\times(1.20) = 0.82$, or an 18% reduction.

Multiple sclerosis

The estimated prevalence of MS in Canada in 2010–2011 was 93,535.[61] The mean cost per MS patient was estimated to be $37,672 in 2009.[62] The total direct cost for MS in Canada in 2016 is estimated at

$$93{,}535 \times \$37{,}672 \times (1.033)\times(0.994)^6 \times(36.3\,\text{million}/34.3\,\text{million}) = \$3.7\,\text{billion}$$

Evidently that estimate does not include lost productivity due to the disease. A recent paper by experts in MS estimated that vitamin D supplementation could prevent 40% of MS cases.[63] Using that value, the total economic burden of MS in Canada could eventually be reduced by $1.5 billion. Although some reduction in MS symptoms appears to be associated with increasing 25(OH)D concentrations, that does not seem to significantly affect the economic burden.[64]

Alzheimer disease and related dementia

AD accounted for 10,000 Canadian deaths/year in 2004–2011.[65] AD and related dementias have an economic burden in Canada of about $16.2 billion, of which about 2-thirds is the total of direct and indirect costs and one-third is the opportunity cost of unpaid caregivers.[66]

A prospective observational study in the US with a mean follow-up of 5.6 y found the hazard ratio for all-cause dementia in 25(OH)D concentrations of < 25 nmol/L vs. > 50 nmol/L of 2.25 (95% CI, 1.23–4.13).[67] The results for AD were similar. Little change occurred for 25(OH)D concentration >50 nmol/L. A second study, reported from Denmark, used findings on serum 25(OH)D concentration from 1981–1983 with follow-up exams in 1991–1993 and 2001–2003.[18] The result is that 7% of dementia could be reduced if everyone had 25(OH)D concentrations >70 nmol/L (Table 6). For an economic burden of $16.2 billion, the economic burden could be reduced by $1.1 billion annually.

Falls, fractures, and musculoskeletal disorders

Osteoporosis accounts for an economic burden of $3.9 billion (2010).[68] On the basis of population increases and inflation, that figure translates to $\$3.9\text{billion}\times (36.3\text{ million}/33.5\text{ million}) \times (1.025)^7 = \$5.0$ billion in 2016 dollars. Vitamin D supplementation can improve osteoporosis and reduce fractures.[26] The classical role of vitamin D is to help with calcium absorption and metabolism, leading to strong bones. The data set chosen to estimate the relation of hip fractures to 25(OH)D concentration comes from Iceland. In that study, 5764 men and women aged 66–96 y were followed up for 5.4 y.[69] Using data for hip fracture rates given in Figure 1 of that study, increasing 25(OH)D concentration to above 100 nmol/L would reduce fracture rates by an estimated 22%.

Other health outcomes

Various studies have reported beneficial effects from vitamin D for several other health outcomes. However, either the 25(OH)D concentration–health outcome relations have not been well characterized or estimating the economic benefit of increasing 25(OH)

D concentrations is difficult. Since these outcomes may also contribute to the beneficial effects of increasing 25(OH)D concentrations for Canadians, we briefly discuss them here.

Dental services cost about $12.6 billion per year in Canada.[70] For children aged 3–14 years, several vitamin D supplementation trials were conducted in the United States and Great Britain between 1928 and 1942.[71] For an average supplementation of about 600 IU/d, the rate of dental caries decreased by half (relative risk = 0.51[95% CI, 0.40–0.65]). However, as noted by Hujoel, the beneficial effects were found for those aged 4–10 y and not for those aged 3 or 11–14 y.[71] A prospective study of tooth loss among male health professionals in the United States found that for those with the highest compared with lowest 25(OH)D concentration, the hazard ratio was 0.86 (95% CI, 0.79–0.93).[72] A related paper found a risk ratio for tooth loss of 0.86 (95% CI, 0.73–1.00) for <52 nmol/L versus 0–50 nmol/L. Tooth loss was reduced by 40% in the elderly over a 2-year period with vitamin D and calcium supplementation.[73]

Mounting evidence indicates that vitamin D reduces risk of major depression disorder (MDD) as well as treats it. A study in the US enrolled community-dwelling black and white subjects between April 1997 and June 1998.[74] More than 800 were enrolled in each of 3 25(OH)D categories:<50 nmol/L, 50–75 nmol/L, and >75 nmol/L. At baseline, the Center for Epidemiologic Studies—Depression (CES-D) Scale was near 3.0 for all 3 groups. After 4 years, unadjusted CES-D scores were near 4.6, 4.8, and 5.5 for low, medium, and high concentrations, respectively. The adjusted hazard ratio for incident depression was 1.65 (95% CI, 1.23–2.22) for people with 25(OH)D <50 nmol/L, compared with those with baseline 25 (OH)D concentration of > 75 nmol/L, and 1.31 (95% CI, 0.99–1.74) for those with baseline 25(OH)D concentration between 50 and 75 nmol/L. A prospective study in Korea found that incidence of depressive symptoms was increased for those individuals with 25 (OH)D concentrations <50 nmol/L compared with those with >50 nmol/L if they had serum total cholesterol levels of < 240 mg/dL (odds ratio [OR] = 1.60 [95% CI, 1.23–2.08]) but not for those with serum total cholesterol >240 ng/dL (OR = 0.97 [95% CI, 0.52–1.81]) after adjustment for confounding variables.[75] A study in Italy conducted a clinical trial with vitamin D for outpatients of mean age 74 ± 6 years with MDD being treated with antidepressant therapy.[76] At the start of the 4-week trial, mean Hamilton Depression Rating Scale scores were 21.1 for the treated cases and 21.5 for the comparison subjects. At the end of 4weeks, the scores were 19.1 and 22, respectively. An 8-week clinical trial of 50,000 IU/wk of vitamin D or placebo was conducted on patients with MDD in Iran from October to December 2014.[77] Baseline 25(OH)D concentrations were 23 ± 15 nmol/L in the placebo group and 35 ± 23 nmol/L in the vitamin D group. At the end of 8weeks, the concentrations were 21 ± 10 nmol/L and 85 ± 23 nmol/L, respectively, and the Beck Depression Inventory total score decreased by 3.2 ± 1.6 in the placebo group and 8.0 ± 1.6 in the vitamin D group.

Inflammatory bowel disease can be either Crohn's disease or ulcerative colitis. The annual economic burden of Crohn's disease in Canada is $1.7 billion, whereas that of ulcerative colitis is $1.2 billion.[78] Several papers have reported inverse correlations between vitamin D status and incidence, prevalence, and/or severity of inflammatory bowel disease.[79,80]

Evidence is mounting that higher 25(OH)D concentrations are associated with better pregnancy and birth outcomes. "The currently available results indicate that vitamin D supplementation during pregnancy reduces the risk of preterm birth, low birth weight, dental caries of infancy, and neonatal infectious diseases such as respiratory infections and sepsis."[81] Furthermore, with unfolding research into fetal origins of pediatric and adult disease, evidence increasingly indicates that gestational vitamin D indices may determine health in later life.[82] For example, an interesting cohort study correlating maternal vitamin D levels at 18 weeks' pregnancy and health outcomes of progeny found that gestational vitamin D deficiency was associated with a higher risk of impaired lung development in 6-year-old offspring, neurocognitive difficulties at age 10 years, increased risk of eating disorders in adolescence, and lower peak bone mass at 20 y.[83]

A recent study concluded that vitamin D is reduces exacerbations of asthma.[84]

All-cause mortality rate

Garland and colleagues[85] presented a meta-analysis of 32 prospective observational studies that investigated all-cause mortality rate with respect to 25(OH)D concentration at time of enrollment. Some studies enrolled community-dwelling people not ill at enrollment, whereas in others, enrolling participants were ill. For the 18 studies with mean age <65 years, the hazard ratio for highest vs. lowest 25(OH)D concentration was 1.8 (95% CI, 1.7–1.9; $p < 0.001$). For the 14 studies with mean age >65 years, the hazard ratiowas 1.5 (95% CI, 1.3–1.6; $p < 0.001$). For the combination, the hazard ratio was 1.8 (95% CI, 1.7–1.8; $p < 0.001$). The meta-analysis found a nearly linear increase in hazard ratio for 25(OH)D concentration <90 nmol/L, with no change above that value. When values derived from Figure 3 in Garland and colleagues are used with the 25(OH)D percentiles, an increase in mortality rate of 30% is found for those aged 50–79 years (Table 7), which translates to a 23% reduction in all-cause mortality rate if those aged 50–79 y had 25(OH)D concentrations >100 nmol/L. That value is higher than the 13%–17% estimated for Europe and the Americas by using 25(OH)D concentration–health outcome relations based largely on incidence rather than mortality rate.[86] The reductions in mortality rates found in that paper translated to about a 2-year mean population increase in life expectancy. Approximately half the deaths in Canada occur in the age range 40–80 y and half for those older than 80 y.[87] In 2011, 242,074 deaths occurred in Canada.[88] For a population increase of 8.4% by 2016, 264,000 deaths would be expected in 2016. Twenty-three percent of those deaths is 60,700. However, deaths for peopleolder than 80 y probably should not be considered premature. For those between the ages of 40 and 80 years, increasing 25 (OH)D concentrations might reduce the premature death rate by 30,000/year.

Results

We estimate that if Canadians raised their mean 25 (OH)D concentrations from 61 to 100 nmol/L, overall it would save 23,000 premature deaths and $12.5 billion annually in direct health care expenses and indirect costs associated with disease. The greatest benefit would accrue to those who currently have 25 (OH)D concentrations below 50 nmol/L, which in Canada is 35% of the population.

The economic burden values for the diseases considered in this study are given in Table 8. The values have been adjusted to 2015 values by using consumer price inflation rates and changes in total population. However, that adjustment is considered conservative because of an underestimate due to increases in population. The total economic burden of the vitamin D–sensitive diseases considered here is estimated at $79.1 billion in 2016 (Table 8). The economic benefit of increasing 25 (OH)D concentrations for all Canadians to above 100 nmol/L is estimated to be $12.5 billion and the estimated reduction in deaths for 2011 is 23,000 (Table 9). That translates to 24,740 deaths in 2016 on the assumption that the death rate remains constant while the population increased by 8.4%. However, the benefits and reductions in premature deaths will be gradually phased in over a decade or so because the estimates are based primarily on prevention of disease, not treatment.

As with all estimates, these have uncertainties, including the 25(OH)D concentration–health outcome relations used; the estimates of economic burdens; whether reducing risk of specific diseases would translate into the same fraction of economic burden; the extent to which changing risk-modifying risk factors such as smoking, alcohol consumption, diet, and obesity modify the relative reduction due to higher 25 (OH)D concentration; and that the analysis omitted several vitamin D–sensitive diseases and conditions because of limited understanding of the effects. Important health outcomes not included are arthritis and rheumatism, autism, Crohn's disease, dental caries, Parkinson disease, adverse pregnancy and birth outcomes, and ulcerative colitis. Estimating how much each of those factors would affect the estimates is difficult. Several other papers also estimated health benefits associated with increased 25(OH)D concentration at the population level. The one for Canada assumed ±50 % uncertainty in the economic burden and mortality rates.[89] One for the Netherlands assumed that the reduction in disease rates due to increasing 25(OH)D concentrations was ±10 %; that is, if the reduction was 25%, the estimated range was 15%–35%, leading to a ± 32%uncertainty in death rates.[90] Two other papers did not provide uncertainty estimates.[86,91] We estimate the uncertainty at ± 50%. The higher estimate is justified on the basis of the finding for deaths for all-cause mortality rate (30,000 deaths/yr) compared with 22,770 deaths/yr for the diseases considered in this work.

Discussion

We estimated the economic costs of diseases in Canada that contributed significantly to overall morbidity and

Table 3. Calculations for CVD for people aged 20–49 y and 50–79 y, using meta-analysis data[15] and annual averaged 25(OH) D concentrations.

Decile	25(OH)D 50–79 y (nmol/L)	CVD, Raise to 100 nmol/L	25(OH)D 20–49 y (nmol/L)	CVD, 100 nmol/L
1	28	1.67	25	1.81
2	35	1.43	32	1.55
3	42.5	1.30	38	1.41
4	50	1.17	45	1.25
5	57.5	1.04	52	1.17
6	65	1.02	58	1.10
7	73	1.00	65	1.05
8	82	1.00	72	1.02
9	90	1.00	82	1.00
10	100	1.00	100	1.00
Sum/10		1.16		1.24

Table 5. Calculations for diabetes mellitus for those aged 20–49 y and 50–79 y, using meta-analysis data[21] and annual averaged 25 (OH)D concentrations.

Decile	25(OH)D 50–79 y (nmol/L)	RR 50–79 y	25(OH)D 20–49 y (nmol/L)	RR 20–49 y
1	28	1.51	25	1.52
2	35	1.44	32	1.45
3	42.5	1.35	38	1.38
4	50	1.27	45	1.31
5	57.5	1.21	52	1.24
6	65	1.12	58	1.18
7	73	1.06	65	1.11
8	82	1.00	72	1.06
9	90	1.00	82	1.00
10	100	1.00	100	1.00
Sum/10		1.20		1.23

RR, relative risk.

mortality. The estimates in Table 9 show a potential large benefit of improving vitamin D status in terms of reduction in economic burden ($12.5billion) and premature deaths (23,000/yr) on the basis of the types of disease for which evidence is strong that higher 25(OH)D concentrations have beneficial effects. The uncertainty in the numbers is about 50% as a result of omitting other diseases with less evidence for vitamin D effects as well as the possibility that the estimates are too high. That uncertainty is supported by the estimate of premature deaths on the basis of the calculation from all-cause mortality rate, 30,000.

Those estimates are similar to those in the previous paper on this topic, which estimated that if the 25 (OH)D concentration of all Canadians were raised from a mean value of 67 nmol/L to 105 nmol/L, the death rate could fall by 37,000 (22,300–52,300 deaths), representing 16.1% (9.7%–22.7%) of annual deaths, and the economic burden could fall by 6.9% (3.8%–10.0%), or $14.4 billion ($8.0 billion–$20.1 billion).[89] That paper considered how vitamin D affects cancer, CVD, DM, falls and fractures, heart disease, influenza and pneumonia, MS, and septicemia as well as pregnancy and birth outcomes. Those estimates were made under the assumption that the mean 25(OH)D concentration would increase and reduce disease rates in proportion to how the mean 25(OH)D concentration moved along the 25(OH)D concentration–health

Table 4. Calculations for breast cancer for those aged 20–49 y and 50–79 y, using meta-analysis data[11] and annual averaged 25 (OH)D concentrations.

Decile	25(OH)D 50–79 y (nmol/L)	Breast cancer 50–79 y	25(OH)D 20–49 y (nmol/L)	Breast cancer 20–49 y
1	28	2.61	25	2.90
2	35	2.29	32	2.33
3	42.5	1.95	38	2.05
4	50	1.70	45	1.76
5	57.5	1.54	52	1.59
6	65	1.39	58	1.44
7	73	1.29	65	1.33
8	82	1.17	72	1.24
9	90	1.07	82	1.12
10	100	1.00	100	1.00
Sum/10		1.60		1.68

Table 6. Calculations for dementia for those aged 50–79 y, using meta-analysis data[18] and annual averaged 25(OH)D concentrations.

Decile	25(OH)D 50–70 y (nmol/L)	Dementia, 50–79 y
1	28	1.22
2	35	1.19
3	42.5	1.15
4	50	1.11
5	57.5	1.07
6	65	1.03
7	73	1.00
8	82	1.00
9	90	1.00
10	100	1.00
Sum/10		1.08

Table 7. Calculations for all-cause mortality rate for those aged 20–49 y and 50–79 y, using meta-analysis data[85] and annual averaged 25(OH)D concentrations.

Decile	25(OH)D 50–79 y (nmol/L)	All-cause Mortality RR 50–79 y	25(OH)D 20–49 y (nmol/L)	All-cause Mortality RR 20–49 y
1	28	1.70	25	1.76
2	35	1.60	32	1.63
3	42.5	1.51	38	1.56
4	50	1.40	45	1.43
5	57.5	1.30	52	1.35
6	65	1.22	58	1.22
7	73	1.16	65	1.19
8	82	1.10	72	1.14
9	90	1.05	82	1.09
10	100	1.00	100	1.00
Sum/10		1.30		1.34

100 nmol/L: 1.00/1.30 = 0.77, or a 23% reduction.

Table 8. Cost estimates for vitamin D–sensitive outcomes; within direct costs including morbidity and mortality and time lost from work.

Outcome	Total direct costs ($M)	Total indirect costs ($M)	Total reported	Year	Total econ ($B) 2016**	Reference
Cancer			6500	2010	7.3	Ref. [44]
CVD			20,900	2008	24.6	Ref. [40]
Dementia			16,200	2016	16.2	Ref. [66]
DM	12,000	3,000	15,000	2015	15.7	Ref. [59]
MS			3770	2009	3.7	Ref. [62]
Osteoporosis			3900	2010	5.0	Ref. [68]
Respiratory infections	2593	2818	5411	2008	6.1	Ref. [55]
Total					78.6	

*, adjusted for inflation.
**adjusted for both population increases and consumer price index inflation.
CVD, cardiovascular disease; DM, diabetes mellitus; MS, multiple sclerosis.

outcome relation. In addition, earlier estimates of the 25(OH)D concentration–health outcomes were used.

Another issue with the estimated values is that they are generally calculated based on observational studies of disease incidence. Many of the diseases have a large prevalence, with new cases added annually while others die or are cured. Thus, the estimates are for the steady-state situation after people have had 25(OH)D concentrations for long periods. For some diseases such as respiratory infections, the beneficial effects start almost immediately. For some intermediate situations, such as cancer, survival rates are better with higher 25(OH)D concentrations.[12,93] Thus, even if all Canadians achieved concentrations of > 100 nmol/L immediately, the beneficial effects would accrue slowly, perhaps over 10–20 y because for many health outcomes, the beneficial effects of vitamin D are much stronger for prevention than for treatment. On the other hand, raising 25(OH)D concentrations does appear to improve the health status of people diagnosed with several diseases, including many cancers, CVD, respiratory tract infections, and MS.

Although the goal of this study was to estimate the economic benefits of increasing 25(OH)D concentrations for all Canadians to >100 nmol/L, there appear to be important benefits if all had concentrations raised to >50 nmol/L and >75 nmol/L. According to the data used for the calculations, raising 25(OH)D concentrations above 50 nmol/L would confer little additional benefit for CVD and dementia. However, such in increase would yield benefits for people with cancer or DM and would improve the all-cause mortality rate. To more fully assess the benefits from raising 25(OH)D concentrations, better understanding of the 25(OH)D concentration–health outcome relations is required, which can come from both observational studies and clinical trials. The framework for analysis presented here can then be used to update the projected benefits.

Limitations of this study

Our results are based on prospective observational studies. The results of observational studies are generally not well-supported by clinical trials of vitamin D supplementation.[94] The primary reason for that lack

Table 9. Estimate of reduction in economic burden in Canada if all inhabitants had 25(OH)D concentrations >100 nmol/L after several years.

Outcome	Total economic burden in 2016 ($B)	Reduction due to improving vitamin D status (%)	Reduction in economic burden due to improving vitamin D status ($B)	Deaths in Canada in 2011 [39]	Reduction in deaths, using deaths for 2011
Cancer	7.3	15	1.1	72,476	10,870
CVD	24.6	14	3.4	60,910	8530
Dementia	16.2	7	1.1	10,000	700
DM	15.7	18	2.8	7194	1290
MS	3.7	40	1.5	500 Ref. [92]	200
Osteoporosis (hip fractures)	5.0	22	1.1		
Respiratory infections	6.1	25	1.5	5767	1440
Total	78.6	15.9	12.5	156,847	23,030

Note: Total deaths in Canada in 2011 were 242,074[88]
$B, billions of dollars; CVD, cardiovascular disease; DM, diabetes mellitus; MS, multiple sclerosis.

of support seems to be that the trials were not well designed, being based largely on the guidelines for pharmaceutical drugs rather than for nutrients.[2] Another worrisome point is that clinical trials have been much more successful when baseline 25(OH)D concentrations were low. For example, 50% of the clinical trials with baseline 25(OH)D concentration <50 nmol/L found beneficial effects of vitamin D on biomarkers of inflammation, whereas only 26% of those with higher baseline 25(OH)D concentrations did.[3] The different results with respect to baseline 25 (OH)D concentration may be due to the limited accuracy of clinical trials but could also be due to considerably less benefit for those with 25(OH)D concentrations above 50 nmol/L. Another limitation of clinical trials is that they are of short duration—generally a few months to a few years—yet chronic diseases may develop slowly over decades, and the half-life of vitamin D is about 3 weeks, requiring several months of supplementation to show benefit. Also, because the estimates are based on 25(OH)D concentration–disease incidence rates, we assumed that raising 25(OH) D concentrations would affect mortality rates in the same way as incidence rates. But some studies found that vitamin D affects mortality rates more than incidence rates.[94] Our estimates also do not take into account prevalence rates for the various diseases. Incidence rates can be anywhere from 5% of prevalence for long-duration chronic diseases to near 100% for short-duration respiratory tract infections. Thus, the estimated beneficial effects of > 100 nmol/L 25(OH)D concentrations may take 10–20 y to be fully realized.

Recommendations

To raise 25(OH)D concentrations of all Canadians to >50, 75, or 100 nmol/L, Canadians would have to take 1000–4000 IU/d of vitamin D_3 and/or spend enough time in the sun with enough skin surface exposed when the solar zenith angle was less than 45°, corresponding to midday hours from May to September. Supplements are recommended because getting vitamin D from foods alone is hard. The average Canadian can obtain only 200–300 IU/d from food alone.[95] The US. Institute of Medicine determined that the upper level of 4000 IU/d of vitamin D_3 was a safe dose without doctor supervision. The institute found no evidence of adverse health effects for the general population for intakes as high as 10,000 IU/d.[96] Given the latitudes of Canada, sun exposure is a good source of vitamin D primarily in the summer and then best near solar noon.[97]

More than12 million Canadians do not meet the minimum vitamin D guidelines of 50 nmol/L put forth by Health Canada.[98] Sun exposure has been recognized as a key factor influencing vitamin D concentrations. According to a Consensus Vitamin D Position Statement published by 7 joint health organizations in the UK, enjoying the sun safely, while taking care not to burn, can help to provide the benefits of vitamin D without unduly raising the risk of skin cancer.[99] However, sun exposure in the UK as well as in Canada is a recommendation for only 5–7 months of the year(except for people traveling to sun destinations during winter months). Artificial sources of UVB could substitute when appropriate solar UVB doses are not available.[100]

UV exposure confers health benefits beyond vitamin D production. One is reduction in blood pressure through liberating nitric oxide from subcutaneous nitrogen stores.[101] Another is that UV may modulate the immune response to psoriasis, asthma, MS, and infection through mechanisms independent of vitamin D.[102] UVB exposure apparently reduces the risk of MS through both vitamin D–dependent and –independent mechanisms.[103]

The concerns regarding risk of skin cancer and melanoma are often overstated in comparison with the benefits of non burning, moderate UV exposure. Two studies found that occupational exposure to sunlight was not associated with increased risk of melanoma. One was a meta-analysis of observational studies.[104] The other was a study of cancer incidence by occupation in Nordic countries.[49]

Conclusions

Many people living in Canada do not have optimal 25 (OH)D concentrations as a result of limited solar UVB exposure and/or not obtaining enough vitamin D from food or supplements. Policies should be devised to overcome those limitations.

Abbreviations

25(OH)D	25-hydroxyvitamin D
AD	Alzheimer disease
CI	confidence interval
CVD	cardiovascular disease
DM	diabetes mellitus

IU international unit
MS multiple sclerosis
UVB ultraviolet B

Disclosure of Potential Conflicts of Interest

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Author contributions

All authors conceived and designed the investigation; SJW analyzed Canadian Health Measures Survey Cycle 3 data; WBG performed the economic calculations that all authors reviewed; all authors helped to write and revise the paper.

ORCID

William B. Grant http://orcid.org/0000-0002-1439-3285
Susan J. Whiting http://orcid.org/0000-0002-7573-0425
Gerry K. Schwalfenberg http://orcid.org/0000-0001-7874-2336
Stephen J. Genuis http://orcid.org/0000-0002-4341-5148

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The Estimated Benefits of Vitamin D for Germany

Zittermann, Journal of Molecular Nutrition & Food Research

Introductory Summary by Representative Paul Seaton

This 2010 expert review examined several national surveys to determine the vitamin D status of Germany and recommended that raising the vitamin D levels of German citizens could save up to € 37.5 billion annually through the prevention of negative health outcomes. Applied to the population of Alaska, that equates to an estimated annually savings of over $404 million or $545 per Alaskan.

Between 40 and 45% of the general population of Germany has insufficient levels of vitamin D, and 15 to 30% are deficient. Nearly 3% of the human genome is regulated by the vitamin D endocrine system. Only 20 minutes of whole body exposure to sunlight three times a week is required for most people of European descent to maintain sufficient levels for this system to function, and yet more than 50% of the population of Germany is insufficient. This is due in part to the fact that from October to April it is impossible to get vitamin D from sun exposure due to the angle of the UV rays. Although there is still some disagreement on what vitamin D level is considered adequate, the vast majority of vitamin D researchers agree that levels below 20 ng/ml (50 nmol/L)[i] are insufficient; this review identifies <10 ng/ml as deficient, 10 to 20 ng/ml as insufficient, 20 to 30 ng/ml as hypovitaminosis, ≥40 ng/ml as adequate, and ≥200 ng/ml as intoxication. Even with the standard of insufficiency set at the low 20 ng/ml, over 50% of adults and 60% of children in Germany are insufficient or deficient in vitamin D. Interestingly, the review found that the mean vitamin D level of newborns was only 10 ng/ml and that 67% of all children between three and seventeen had levels under 20 ng/ml, and yet in children under the age of three the rate of insufficiency or deficiency was only 38%. This change in vitamin D status can likely be attributed to the fact that 30% of German children under three are receiving vitamin D supplements as a recommended measure to prevent rickets, but universal vitamin D supplementation is not currently recommended in other age groups in Germany even though many appear to be insufficient or deficient.

The review author calculated the economic cost of low vitamin D based on similar calculations for all of Europe. Using the annual economic burden of various diseases and the rate of risk reduction of these diseases through sufficient vitamin D levels, it is estimated that € 38 billion could be saved annually. After adjusting for the cost of pensions paid to Germans saved from premature death, the cost savings from sufficient vitamin D levels are estimated at € 37.5 billion annually. With a population of 82 million, this equals healthcare savings of € 457 ($545) per German citizen. To maintain a vitamin D level above 30 ng/ml in almost all patients requires a daily intake at or above 4000 IU (100 μg[ii]) but the current mean daily vitamin D intake in German adults is only 40-130 IU. The author advocates for a change in policy allowing for controlled periods of real or artificial sunlight exposure and for Germany to increase the reference value for vitamin D to at least 1000 IU per day.

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[i] This article uses nmol/L to measure vitamin D status, whereas ng/ml is the more common unit in the United States. The conversion factor for ng/ml to nmol/L is 2.5; multiple the ng/ml value by 2.5 to get the estimated nmol/L value or divide the nmol/L value by 2.5 to determine the ng/ml value. For clarity, the nmol/L values of the article have been converted to ng/ml for this summary introduction.

[ii] This article uses micrograms (μg) to describe vitamin D intake amounts, whereas the common US value is international units (IU). 1 μg equals 40 IU. For clarity, this conversion has already been done in this summary.

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The estimated benefits of vitamin D for Germany.

Zittermann, A.

Abstract

This article gives an overview of the vitamin D status in Germany, provides evidence for an independent association of vitamin D deficiency with various chronic diseases, and discusses preventive measures for improving vitamin D status in Germany. The prevalence of vitamin D insufficiency is 40-45% in the general German population. An additional 15-30% are vitamin D deficient. Vitamin D can prevent falls and osteoporotic fractures in older people. There is also accumulating evidence that vitamin D may prevent excess mortality and may probably prevent some chronic diseases that occur in early life such as type 1 diabetes and multiple sclerosis. Adherence to present sun safety policy (avoidance of the sun between 11 am and 3 pm) and dietary recommendations (5-10 micrograms daily for adults) would, however, definitively lead to vitamin D deficiency. The estimated cost saving effect of improving vitamin D status in Germany might be up to 37.5 billion euro annually. It should be the goal of nutrition and medical societies to erase vitamin D deficiency in Germany within the next 5-10 years. To achieve this goal, the daily production of at least 25[1] micrograms of vitamin D in the skin or an equivalent oral intake should be guaranteed.

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[1] One microgram (μg) is equal to 40 international units (IU). 25 μg equals 1000 IU.

Impact of Vitamin D Deficiency on the Productivity of a Health Care Workforce

Plotnikoff et al., Journal of Occupational & Environmental Medicine

Introductory Summary by Representative Paul Seaton

Dr. Platnikoff examined the connection between vitamin D deficiency and employee presenteeism, when an employee is at work but has reduced productivity due to illness, and found that low vitamin D correlated directly with reduced productivity. Presenteeism can be costly to employers. This study found that savings from improved levels of vitamin D range from $112 to $370 per employee if they attain a level greater than 40 ng/ml, depending on their initial vitamin D status and the level they achieve. With over 17,000 active Alaska state employees, improving the vitamin D status of state employees could lead to state productivity cost savings of $1.9 to $6.4 million annually.

Research has shown that employee health status significantly impacts productivity and the cost of that lost productivity can exceed the cost of pharmacy and medical utilization or of illness-related absenteeism. Presenteeism, where employees are physically present at work but demonstrate reduced productivity and/or performance due to illness, constitutes 14% to 73% of total employer health care costs. Through a Health Risk Appraisal (HRA) and a vitamin D test, Dr. Plotnikoff analyzed the rate of presenteeism and the vitamin D status of 10,646 employees in the Allina Health Care system. He found that vitamin D levels were directly related to productivity loss, a correlation that remained significant even at levels of 40 ng/ml. Getting all of the workforce above 20 ng/ml would save .19% of total payroll cost, above 30 ng/ml would save .55%, and above 40 ng/ml would save .63% of pay roll cost. At 40 ng/ml this amounted to a $7.8 million dollar annual savings for this employer alone. At $370 per employee at the 40 ng/ml level, the potential savings from correcting vitamin D deficiency dwarf the costs of presentism due to upper repertory tract infections ($134 per employee), cancer ($144 per employee), and diabetes ($257 per employee). Almost 29% of the employees tested had vitamin D levels below 20 ng/ml, the level recommended by the Institute of Medicine (IOM) for bone health. 60.8% were below 30 ng/ml, a level recognized by many medical associations as the lower range of vitamin D sufficiency. Employee response to the HRA was highly positive, indicating that a vitamin D assessment and health promotion campaign as a part of an employee HRA may represent a low-cost, high-return program to reduce presenteeism and total employer healthcare costs.

Nearly 30% of health care workers had serum levels below the IOM recommended 20 ng/ml and only 41.3% reported taking any vitamin D supplements. This is particularly surprising considering that the participating employees were physicians, nurses, and pharmacists; given the abundance of literature on the subject, you could expect that health care professionals would be more aware of the dangers of low vitamin D and would have higher levels. If health care workers missed these messages and are vitamin D deficient, then their patients may also be at higher risk for unrecognized deficiency.

Impact of Vitamin D Deficiency on the Productivity of a Health Care Workforce

Gregory A. Plotnikoff, MD, MTS, Michael D. Finch, PhD, and Jeffery A. Dusek, PhD

Objective: To define the relationship between vitamin D status and employee presenteeism in a large sample of health care employees. **Methods:** Prospective observation study of 10,646 employees of a Midwestern-integrated health care system who completed an on-line health risk appraisal questionnaire and were measured for 25-hydroxyvitamin D. **Results:** Measured differences in productivity due to presenteeism were 0.66, 0.91, and 0.75 when comparing employees above and below vitamin D levels of 20 ng/mL, 30 ng/mL, and 40 ng/mL, respectively. These productivity differences translate into potential productivity savings of 0.191%, 0.553%, and 0.625%, respectively, of total payroll costs. **Conclusions:** Low vitamin D status is associated with reduced employee work productivity. Employee vitamin D assessment and replenishment may represent a low-cost, high-return program to mitigate risk factors and health conditions that drive total employer health care costs.

Learning Objectives

- Discuss the reasoning behind the suggestion that vitamin D deficiency may be a "fundamental risk factor" for reduced work productivity.
- Summarize the newly reported associations between vitamin D status and productivity, including the potential productivity savings for employees at different vitamin D levels.
- Review the study implications for employee health risk assessments and efforts to address risk factors for presenteeism and high health costs.

Employee health status significantly impacts workplace productivity and overall business performance.[1] Increasingly, employers are concerned not only with direct health care costs but also with indirect costs due to employee presenteeism, the state when employees are physically present at work but demonstrate reduced productivity and/or performance due to illness.[2] Presenteeism is financially significant: the cost to employers for presenteeism can exceed even the costs of pharmacy and medical utilization, illness-related absenteeism, or disability.[3] Presenteeism, not absenteeism or disability, accounts for the majority of lost productive time due to both pain conditions[4] and depression.[5] Surprisingly, for 18 common health conditions, presenteeism alone contributes 14% to 73% to total employer health care costs.[3] Presenteeism may cost US employers more than $150 billion per year.[6]

Presenteeism costs are not addressable by employer shifts to higher insurance co-pays and deductibles for both pharmacy and medical costs. The greatest opportunities to reduce presenteeism costs may come from employee health promotion programs such as health risk appraisals (HRAs), disease management programs, and behavior modification programs.[7] From these platforms, targeted investment in reduction of a fundamental risk factor among employees may deliver a powerful return through productivity gains.

Vitamin D deficiency may represent one such fundamental risk factor. Vitamin D deficiency is associated with the numerous conditions that can result in presenteeism,[8] including chronic nonspecific musculoskeletal pain,[9,10] low back pain,[11–13] allergic rhinitis,[14] arthritis,[15–18] asthma,[19–21] cancer,[22–26] depression,[27–30] diabetes,[31,32] gestational diabetes,[33] heart disease,[34,35] hypertension,[36,37] migraine/headache,[38] and respiratory disorders.[39–42] Additional associations related to impaired productivity may include impaired cognition,[43,44] falls,[45] and bone fractures.[46] For many of these conditions, there is an inverse relationship between vitamin D status and either disease activity or functional capacity.

Given these relationships, we hypothesized that vitamin D status may be associated with employee presenteeism. To test this hypothesis, we measured both vitamin D status and workplace productivity (presenteeism) across a large health care system as one part of an annual employee HRA.

METHODS

Participants

As part of an annual Employee Wellness campaign, 20,692 benefits-eligible employees of the Allina Health Care system in Minnesota and western Wisconsin were invited to complete an on-line HRA. Data were collected between January 1 and February 15, 2010. Respondents received $50 in compensation. Employees who completed the supplemental HRA and provided a blood sample to measure their vitamin D level between February 1 and April 1, 2010, were given a $25 gift card.The Allina Hospital and Clinics institutional review board reviewed and approved this protocol prior to any study procedures taking place.

Measures

As part of the HRA, respondents were asked their age, sex, height, weight, race, job classification, vitamin and dietary supplement intake, marital status, and medical history. The HRA also included the validated Workplace Productivity and Activity Impairment (WPAI) Questionnaire[47] that measures work limitations experienced in the prior 7 days as a result of physical or emotional health problems. The WPAI was created and has been used to measure the amount of presenteeism attributable to general health.[47]

All vitamin D measurements were performed at the Allina central laboratory using the LIAISON 25-OH Vitamin D Assay (DiaSorin, Inc, Stillwater, MN), a direct competitive chemiluminescence immunoassay for quantitative determination of total 25-OH

From the Center for Health Care Innovation and Penny George Institute for Health and Healing (Drs Plotnikoff and Dusek), Allina Hospitals and Clinics; and University of Minnesota Carlson School of Management (Dr Finch), Minneapolis, Minn.

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Address correspondence to: Gregory A. Plotnikoff, MD, MTS, Allina Center for Health Care Innovation, Abbott Northwestern Hospital, 800 E. 28th St, Minneapolis, MN 55407. E-mail: gregory.plotnikoff@allina.com.

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vitamin D in serum. The coefficient of variability for vitamin D was 12.5% at a level of 15.0 ng/mL and 9.8% at a level of 50.0 ng/mL.

Analysis Procedures

The method for estimating presenteeism from the WPAI has been described previously.[48] In brief, participants were asked, How much do health problems affect productivity while working? On a scale of 0 to 10, participants were instructed to choose a low number if health problems affected their work only a little. Nevertheless, if they determined that their health problems affected their work a great deal, then they were to choose a large number. The participants' presenteeism score is derived when this answer is multiplied by 10 to derive an overall percentage of presenteeism. Each participant's score has a possible range from 0% to 100%. Separate Welch's *t* tests[48] were employed to assess for differences in mean presenteeism by levels of 25-OH vitamin D sufficiency suggested in the current medical literature (>20 ng/mL, >30 ng/mL, and >40 ng/mL).[49,50] Welch's *t* test was employed because of heteroscedasticity.

RESULTS

Of the 20,692 benefits-eligible employees, 14,835 (71.7%) responded to the supplemental HRA. A total of 10,646 employees (51.4%) completed the HRA and provided a blood sample for measurement of 25-OH vitamin D. There were no differences on demographic variables between the group of employees completing just the HRA and the group of participants completing both assessments (Table 1).

The average 25-OH vitamin D level was 28.1 ng/mL (SD = 13.6). Further examination revealed that 6.0% of participants (n = 643) had values lower than 10 ng/mL, 28.9% (n = 2943) were below 20 ng/mL, 60.8% (n = 6198) had values lower than 30 ng/mL, and 83.5% (n = 8512) were lower than 40 ng/mL. A total of 41.3% of participants reported vitamin D supplementation including vitamin D obtained from multivitamins. Of that, 17.8% reported supplementation of more than 1000 IU daily, 6.1% took more than 2000 IU daily, and 2.1% ingested more than 4000 IU every day.

The overall mean presenteeism score for employees was 5.11 (SD = 12.27). The spectrum of presenteeism scores is illustrated by the average presenteeism score for participants with 25-OH vitamin D levels lower than 20 ng/mL of 5.58 (SD = 12.99) and the mean score for those employees with a serum level of 40 ng/mL or higher was 4.48 (SD = 11.24). As shown in Table 2, participants with 25-OH vitamin D levels of 20 ng/mL or higher had significantly lower presenteeism than employees with 25-OH vitamin D levels of lower than 20 ng/mL ($P = 0.014$). Furthermore, this relationship also was significant for comparisons at vitamin D states of lower than 30 ng/mL and 30 ng/mL or higher ($P = 0.0001$) as well as lower than 40 ng/mL and 40 ng/mL or higher ($P = 0.022$).

We also calculated the percentage of payroll (and the dollar amount) lost to presenteeism due to differences in presenteeism for these same groups. These results are shown in the two rightmost columns of Table 2. To illustrate, for the cutoff value of 20 ng/mL, 2943 employees (28.9%) had 25-OH vitamin D levels of lower than 20 ng/mL, and there was a 0.66 absolute difference in presenteeism in the lower than 20 ng/mL group (5.58 to 4.92). Multiplying the absolute difference by the percentage of employees with levels of lower than 20 ng/mL yields the potential percentage of total payroll the employer lost because of differences in presenteeism. For the 20 ng/mL example, this yields a value of 0.19% per employee; for an overall payroll of $1.228 billion for this employer, this difference translates to a potential cost savings of $2.3 million or roughly $112 per employee per year. Significantly, these potential cost savings increase at higher 25-OH vitamin D cutoff values: $326 per employee at a cutoff of 30 ng/mL ($6.8 million) and $370 per employee at 40 ng/mL ($7.7 million). (Fig. 1)

TABLE 1. Sample Characteristics

	Completed HRA Only (n = 14,835)	Completed HRA With Vitamin D Assessment (n = 10,646)
Unknown	0.1	0.5
Some other race	3.1	0.8
Black or African American	4.2	3.3
White	89.4	90.9
Asian or Pacific Islander	1	2.8
American Indian or Alaska Native	0.1	0.5
Chose not to answer	1.7	1.5
Hispanic origin	1.4	1.3
Not of Hispanic origin	89	89.2
Chose not to answer	9.6	9.5
Administrative support	12.5	13.3
Labor or production	2.1	1.9
Professional/management	46.9	45.9
Retired	0	0
Sales	0.1	0.1
Service	7.2	6.9
Skilled craft	2	1.9
Student	0.6	0.4
Technical	13.2	13.9
Other	15.5	15.6
Age, %		
18–39	0.1	0
20–29	16.2	14.9
30–39	23.9	22.7
40–49	25.4	25.7
50–59	26.4	28
60–64	6.2	8.3
≥65	1.8	0.4
Mean age (SD)	43.2 (11.7)	44.3 (11.6)
Female, %	84.7	87.9

DISCUSSION

This study of 10,646 health care employees represents the largest cross-sectional study of employer-based 25-OH vitamin D status and on-the-job productivity to date. The average presenteeism score for our health care employees was just more than 5%, which is comparable to prior reports in which presenteeism ranged from 2% for healthy populations[5,51] to 29% for those with allergies[52] and upward of 40% for individuals with pain.[4]

Importantly, our results suggest that increasing levels of 25-OH vitamin D are associated with significantly improved on-the-job productivity, with the best response at serum 25-OH vitamin D levels greater than 40 ng/mL. This serum level is significantly higher than the level of 20 ng/mL recommended by the Institute of Medicine for bone health.[49] Nevertheless, values greater than 20 ng/mL are consistent with other recommendations for optimal outcomes in the peer-reviewed literature.[50]

The resulting data are economically significant: increasing vitamin D status correlates with increasing on-the-job productivity (reduced presenteeism). For the specific health care employee population studied, the potential employer savings range from a low of 0.19% to a high of 0.63% of total payroll costs depending on the cutoff value of 25-OH vitamin D chosen from 20 ng/mL, 30 ng/mL, or 40 ng/mL (Fig. 2). For this employer, this translates

TABLE 2. Mean Presenteeism and Potential Cost Savings by Threshold Vitamin D Levels

Vitamin D (ng/mL)	n	Employees Less Than Cutoff Value, %	Mean Presenteeism Percentage (SD)	Absolute Difference in Presenteeism, %	Potential Payroll Lost, %	Potential Cost Savings Per Employee	Payroll Equivalent
<20	2943	28.9	5.58 (12.99)	0.66*	0.19	$112	$2.33 million
≥20	7256		4.92 (11.96)				
<30	6198	60.8	5.46 (12.93)	0.91**	0.55	$326	$6.78 million
≥30	4001		4.55 (11.15)				
<40	8512	83.5	5.23 (12.46)	0.75*	0.63	$370	$7.68 million
≥40	1687		4.48 (11.24)				

*$P < 0.05$; **$P < 0.001$.

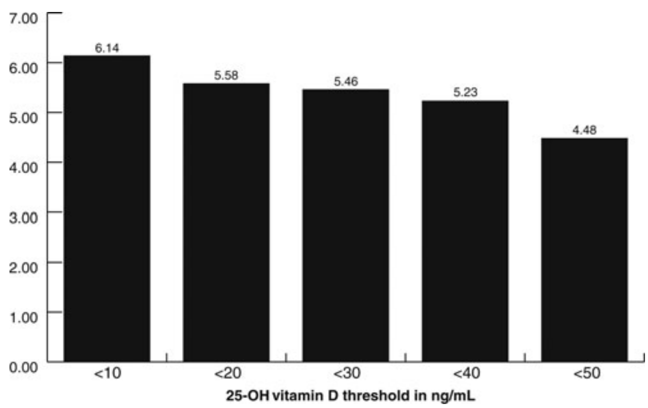

FIGURE 1. Presenteeism by 25-OH vitamin D thresholds.

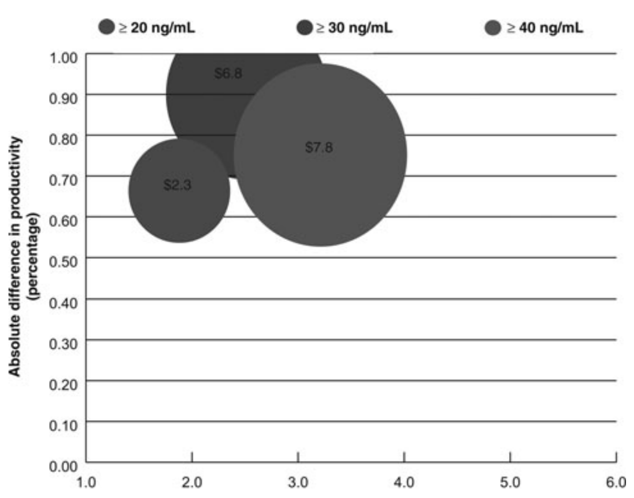

FIGURE 2. Potential payroll savings at study site by achieving suggested levels of vitamin D (in millions).

into potential savings in productivity costs ranging from more than $2.3 million ($112 per employee) to nearly $7.8 million ($370 per employee). For 25-OH vitamin D levels higher than 30 ng/mL, the per employee costs are comparably favorable to 2004 presenteeism cost estimates for the medical conditions with the greatest impact on presenteeism costs including allergy at $271.04, arthritis at $326.88, depression/sadness/mental illness at $348.04, diabetes at $256.91, and migraine/headache at $213.78. These potential savings per employee are significantly better than the estimated presenteeism costs for asthma ($99.55), respiratory tract infections ($133.84), and any cancer ($144.01).[8] This study's findings suggest a significant return on investment for cost-conscious employers given the relative simplicity of 25-OH vitamin D testing and supplementation.

There are several potential limitations to this study. First, employee productivity was measured as presenteeism by the WPAI, a retrospective self-report on the previous week, which may be subject to recall bias. Nevertheless, the WPAI is a widely accepted and validated instrument for measuring productivity.[47] A second limitation is the use of single assessment at one point in time for both the WPAI and vitamin D as the measurement of productivity and vitamin D status throughout the year. With the change of seasons, both health status, such as with allergies and influenza, and vitamin D status may change.[53] Although there is predictive value in snapshots, this limitation highlights the need for long-term prospective studies.

A third limitation may be reduced generalizability to institutions whose employees have vastly different demographic profiles than the current system with employees who are overwhelmingly white and female. These findings may not generalize to different sex and minority status, locations, and/or occupations. Generalizability also may be limited because Minnesota's health care workforce has a relatively high risk of vitamin D deficiency, including wearing ultraviolet B protective lotions, working long hours indoors, and living at a northern latitude where sun exposure for half the year is insufficiently strong to induce vitamin D formation in skin. Nevertheless, the percentages of participants in this study with levels lower than 10 ng/mL, lower than 30 ng/mL, and higher than 30 ng/mL are consistent with National Health and Nutrition Examination Survey data from 2000 to 2004 and, as such, concerns with generalizability may be a nonissue.[54]

Nearly 30% of the health care workers tested had serum 25-OH vitamin D levels lower than the 20 ng/mL recommended by the Institute of Medicine.[49] This surprisingly low vitamin D status needs to be better understood. One potential reason may be the testing in late winter when serum levels are expected to be at their lowest values. We anticipated that health care workers would be more likely to supplement during winter months in Minnesota (>43° north latitude) when solar vitamin D production is not possible. Nevertheless, only 41.3% of participants reported taking any supplemental vitamin D at all, including multivitamins. This low rate is surprising for both the general employee population and the health care professional population. Between 2007 and the start of this study, the general public in Minnesota was exposed to significant radio, television, and newspaper coverage on vitamin D deficiency as an important public health concern. Minnesota's largest newspaper alone, which reaches 1.6 million metropolitan adults, ran 15 articles about vitamin D during this time including a large front-page Sunday article[55] accompanied by a Web-based video and interactive blog. The results were also surprisingly low for this population of physicians, nurses, and pharmacists given the numerous editorials and commentaries in leading international medical journals since 1998 that have urged physicians to recognize and address vitamin D deficiency in their patients.[56–63] Specific to Minnesota, since 1996, four public health commentaries in *Minnesota Medicine*, the journal of the Minnesota Medical Association, have addressed vitamin D deficiency.[64–67] Significantly, if health care workers, including physicians, nurses, and pharmacists, missed these messages and are vitamin D deficient, then their patients may also be at higher risk for unrecognized deficiency.

These data suggest that an employee vitamin D assessment and replenishment campaign may represent a low-cost, high-return program to mitigate risk factors and health conditions that drive total employer health care costs. The strongly positive employee response to this study demonstrates the practical feasibility of including a vitamin D assessment with an employee HRA and health promotion campaign. Future research should include a prospective intervention to assess the effect of vitamin D status change on presenteeism as well as health care utilization.

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