





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 <sup>a</sup>, Susan J. Whiting <sup>b</sup>, Gerry K. Schwalfenberg <sup>c</sup>, Stephen J. Genus <sup>d</sup>, and Samantha M. Kimball<sup>e</sup>

<sup>a</sup>Sunlight, Nutrition, and Health Research Center, San Francisco, CA, USA; <sup>b</sup>College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Canada; <sup>c</sup>Department of Family Medicine, University of Alberta, Edmonton, Alberta, Canada; <sup>d</sup>Faculty of Medicine at the University of Alberta, Edmonton, Alberta, Canada; <sup>e</sup>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.<sup>1</sup> 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

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

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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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).<sup>5</sup> 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,<sup>6,7</sup> CVD,<sup>8</sup> and MS.<sup>9</sup>

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](http://pubmed.gov) and [scholar.google.com](http://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)<sup>35</sup> 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](http://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.<sup>36</sup>

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.<sup>37</sup> The consumer price index increased from 97.8 in 2001 to 126.6 in 2015.<sup>38</sup> 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).<sup>39</sup> 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.<sup>40</sup> 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<sup>41</sup> and the population distribution in Canada in 2014,<sup>42</sup> 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.<sup>43</sup>

The total economic effect of cancer in 2010 was \$6.5 billion,<sup>44</sup> 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

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

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.<sup>11</sup> Breast cancer incidence rates have a risk of about 0.55 for high vs. low 25(OH)D concentration and short follow-up times.<sup>11</sup> Pancreatic cancer incidence inversely correlated with 25(OH)D concentration in a pooled analysis from 5 cohort studies.<sup>45</sup> For lung cancer, a study in Denmark found a 20% increased risk of lung cancer for a 50% reduction in 25(OH)D concentration.<sup>46</sup> 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.<sup>47</sup>

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<sub>3</sub> plus 1500 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.<sup>13</sup> 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.<sup>48</sup> In Nordic countries, smoking and UVB exposure contributed nearly equally to

cancer risk for males.<sup>49</sup> 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.<sup>47</sup> 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.<sup>50</sup> 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.<sup>51</sup> 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.<sup>52</sup>

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.<sup>53</sup>

### Respiratory infections

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

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

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<sub>3</sub> developed a cold or influenza, compared with 8 taking 800 IU/d and 30 taking a placebo.<sup>32</sup> 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<sub>3</sub> supplementation was 2000 IU/d, and the achieved 25(OH)D concentration was 89 ± 23 nmol/L.<sup>56</sup> 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<sub>3</sub> 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]).<sup>33</sup> 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<sub>3</sub> 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).<sup>34</sup> 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,<sup>57</sup> one from the US<sup>31</sup> 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<sub>3</sub>, compared with 234 students taking a placebo.<sup>58</sup> 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 than 3 million Canadians and is responsible for an economic burden of \$15.4 billion in 2015<sup>59</sup> (\$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.<sup>21</sup> 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,<sup>42</sup> 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.<sup>61</sup> The mean cost per MS patient was estimated to be \$37,672 in 2009.<sup>62</sup> 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.<sup>63</sup> 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.<sup>64</sup>

### **Alzheimer disease and related dementia**

AD accounted for 10,000 Canadian deaths/year in 2004–2011.<sup>65</sup> 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.<sup>66</sup>

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).<sup>67</sup> 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.<sup>18</sup> 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).<sup>68</sup> On the basis of population increases and inflation, that figure translates to  $\$3.9 \text{ billion} \times (36.3 \text{ million} / 33.5 \text{ million}) \times (1.025)^7 = \$5.0 \text{ billion}$  in 2016 dollars. Vitamin D supplementation can improve osteoporosis and reduce fractures.<sup>26</sup> 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.<sup>69</sup> 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.<sup>70</sup> For children aged 3–14 years, several vitamin D supplementation trials were conducted in the United States and Great Britain between 1928 and 1942.<sup>71</sup> 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.<sup>71</sup> 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).<sup>72</sup> 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.<sup>73</sup>

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.<sup>74</sup> 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.<sup>75</sup> A study in Italy conducted a clinical trial with vitamin D for outpatients of mean age  $74 \pm 6$  years

with MDD being treated with antidepressant therapy.<sup>76</sup> 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 4 weeks, 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.<sup>77</sup> Baseline 25(OH)D concentrations were  $23 \pm 15$  nmol/L in the placebo group and  $35 \pm 23$  nmol/L in the vitamin D group. At the end of 8 weeks, the concentrations were  $21 \pm 10$  nmol/L and  $85 \pm 23$  nmol/L, respectively, and the Beck Depression Inventory total score decreased by  $3.2 \pm 1.6$  in the placebo group and  $8.0 \pm 1.6$  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.<sup>78</sup> Several papers have reported inverse correlations between vitamin D status and incidence, prevalence, and/or severity of inflammatory bowel disease.<sup>79,80</sup>

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."<sup>81</sup> 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.<sup>82</sup> 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.<sup>83</sup>

A recent study concluded that vitamin D reduces exacerbations of asthma.<sup>84</sup>

#### **All-cause mortality rate**

Garland and colleagues<sup>85</sup> 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 ratio was 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.<sup>86</sup> 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.<sup>87</sup> In 2011, 242,074 deaths occurred in Canada.<sup>88</sup> 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 people older 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  $\pm 50\%$  uncertainty in the economic burden and mortality rates.<sup>89</sup> One for the Netherlands assumed that the reduction in disease rates due to increasing 25(OH)D concentrations was  $\pm 10\%$ ; that is, if the reduction was 25%, the estimated range was 15%–35%, leading to a  $\pm 32\%$  uncertainty in death rates.<sup>90</sup> Two other papers did not provide uncertainty estimates.<sup>86,91</sup> We estimate the uncertainty at  $\pm 50\%$ . 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<sup>15</sup> 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

mortality. The estimates in Table 9 show a potential large benefit of improving vitamin D status in terms of reduction in economic burden (\$12.5 billion) 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).<sup>89</sup> That paper considered how vitamin D affects cancer,

**Table 4.** Calculations for breast cancer for those aged 20–49 y and 50–79 y, using meta-analysis data<sup>11</sup> 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 5.** Calculations for diabetes mellitus for those aged 20–49 y and 50–79 y, using meta-analysis data<sup>21</sup> 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.

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 6.** Calculations for dementia for those aged 50–79 y, using meta-analysis data<sup>18</sup> and annual averaged 25(OH)D concentrations.

Decile	25(OH)D 50–79 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<sup>85</sup> 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. <sup>44</sup>
CVD			20,900	2008	24.6	Ref. <sup>40</sup>
Dementia			16,200	2016	16.2	Ref. <sup>66</sup>
DM	12,000	3,000	15,000	2015	15.7	Ref. <sup>59</sup>
MS			3770	2009	3.7	Ref. <sup>62</sup>
Osteoporosis			3900	2010	5.0	Ref. <sup>68</sup>
Respiratory infections	2593	2818	5411	2008	6.1	Ref. <sup>55</sup>
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.<sup>12,93</sup> 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 an 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.<sup>94</sup> 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 <sup>39</sup>	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. <sup>92</sup>	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<sup>88</sup>

\$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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>94</sup> 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<sub>3</sub> 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.<sup>95</sup> The US. Institute of Medicine determined that the upper level of 4000 IU/d of vitamin D<sub>3</sub> 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.<sup>96</sup>

Given the latitudes of Canada, sun exposure is a good source of vitamin D primarily in the summer and then best near solar noon.<sup>97</sup>

More than 12 million Canadians do not meet the minimum vitamin D guidelines of 50 nmol/L put forth by Health Canada.<sup>98</sup> 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.<sup>99</sup> 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.<sup>100</sup>

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

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.<sup>104</sup> The other was a study of cancer incidence by occupation in Nordic countries.<sup>49</sup>

### 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

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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. Genus  <http://orcid.org/0000-0002-4341-5148>

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