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REVIEW

An estimate of the global reduction in mortality rates through doubling vitamin D levels

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Background/Objectives: The goal of this work is to estimate the reduction in mortality rates for six geopolitical regions of the world under the assumption that serum 25-hydroxyvitamin D (25(OH)D) levels increase from 54 to 110 nmol/l.
Subjects/Methods: This study is based on interpretation of the journal literature relating to the effects of solar ultraviolet-B (UVB) and vitamin D in reducing the risk of disease and estimates of the serum 25(OH)D level–disease risk relations for cancer, cardiovascular disease (CVD) and respiratory infections. The vitamin D-sensitive diseases that account for more than half of global mortality rates are CVD, cancer, respiratory infections, respiratory diseases, tuberculosis and diabetes mellitus. Additional vitamin D-sensitive diseases and conditions that account for 2 to 3% of global mortality rates are Alzheimer's disease, falls, meningitis, Parkinson's disease, maternal sepsis, maternal hypertension (pre-eclampsia) and multiple sclerosis. Increasing serum 25(OH)D levels from 54 to 110 nmol/l would reduce the vitamin D-sensitive disease mortality rate by an estimated 20%.
Results: The reduction in all-cause mortality rates range from 7.6% for African females to 17.3% for European females. Reductions for males average 0.6% lower than for females. The estimated increase in life expectancy is 2 years for all six regions.
Conclusions: Increasing serum 25(OH)D levels is the most cost-effective way to reduce global mortality rates, as the cost of vitamin D is very low and there are few adverse effects from oral intake and/or frequent moderate UVB irradiance with sufficient body surface area exposed.
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Introduction

Research on the health benefits of vitamin D has grown explosively during the past decade. According to the National Library of Medicine's PubMed database (www.pubmed.gov), as of 5 March 2011, 28 208 papers with vitamin D in the title or abstract have been published since 1922, with 14 908 published from 2000 to present and 4876 from 2009 to present. The driving reason for this explosive growth of interest seems to be that vitamin D has many benefits; nearly every cell in the body has a vitamin D receptor (Bikle, 2011). The original purpose of vitamin D was evidently for calcium regulation: 'Vitamin D signalling evolved to enable the organism to effectively regulate calcium flux, storage and signalling and that such regulation is critical for the evolutionary process' (Bikle, 2011). The importance of vitamin D for human health is apparent in the evolution of human skin color around the world, with dark skin required in the tropical plains to protect against folate destruction and damage from free radical production, and pale skin required at high latitudes to produce vitamin D as efficiently as possible. The ability to tan to change skin pigmentation arose in the mid-latitude region to accommodate seasonal changes in solar ultraviolet (UV) doses (Jablonski and Chaplin, 2010).

Studies have looked at vitamin D's health benefits for many types of disease. Several recent reviews discuss the health benefits of vitamin D (Grant and Boucher, 2011; Grant and Peiris, 2010; Holick, 2007, 2011; Norman, 2008). In a project under way for the Vitamin D Council (San Luis Obispo, CA, USA), I have identified ~100 types of disease for which low serum 25-hydroxyvitamin D (25(OH)D) increases risk of incidence or premature death or for which some of the standard drug or surgical treatments reduce serum 25(OH)D levels. These documents should be online (www.vitamindcouncil.org) by the end of May 2011.

One can use data from the World Health Organization on annual death rates by type of disease or other cause to

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Table 1 Global annual death rates for 2004 from diseases linked to low serum 25-hydroxyvitamin D (25(OH)D) levels (WHO, 2008)

Cause or disease	*Male deaths (× 1000)*	*Female deaths (× 1000)*
Cardiovascular diseases	8338	8735
Malignant neoplasms	4154	3270
Respiratory infections	2207	2052
Respiratory diseases	2155	1881
Tuberculosis	969	494
Diabetes mellitus	508	633
Alzheimer's disease	181	312
Falls	260	164
Meningitis	181	159
Parkinson's disease	58	52
Maternal sepsis		62
Maternal hypertension		62
Multiple sclerosis	7	11
Vitamin D sensitive	19 018	17 887
(All causes)	31 082	27 690
Vitamin D (% of all)	61	65

Musculoskeletal diseases: rheumatoid arthritis, osteoarthritis, gout, low back pain, other. Respiratory diseases: chronic obstructive pulmonary disease, asthma, other.

estimate reductions in mortality rates from higher serum 25(OH)D levels. Table 1 (WHO, 2008) gives the global annual death rates from diseases linked to low serum 25(OH)D levels. The top six types of vitamin D-sensitive disease—cardiovascular disease (CVD), malignant neoplasms (cancer), respiratory infections, respiratory diseases, tuberculosis (TB) and diabetes mellitus—account for 59% of male deaths and 62% of female deaths globally. Another seven vitamin D-sensitive diseases add 2 to 3% to the death rates related to vitamin D deficiency. The data are available by geopolitical region for the six regions of the world: Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia and Western Pacific.

Papers outlining the evidence for vitamin D in reducing the burden of diseases with the highest mortality rates for which vitamin D reduces incidence and mortality rates include those for CVD (Parker *et al*., 2010), cancer (Garland *et al*., 2009), bacterial and viral respiratory infections (Cannell *et al*., 2006; Liu *et al*., 2007), chronic obstructive pulmonary disease (COPD; Black and Scragg, 2005), tuberculosis (TB; Liu *et al*., 2007), diabetes (Parker *et al*., 2010; Pittas *et al*., 2010), musculoskeletal diseases leading to falls (Cauley *et al*., 2008; Pfeifer *et al*., 2009) and dementia (Grant, 2009a).

Several estimates on the reduction of mortality rates and/or economic burden of disease based on the major vitamin D-sensitive diseases have been published for North America (Grant, 2009b; Grant *et al*., 2010) and Europe (Grant *et al*., 2009, 2011; Grant and Schuitemaker, 2010). For these countries, raising mean population serum 25(OH)D levels from 50–70 nmol/l to 105–112 nmol/l could reduce the all-cause mortality rate by an estimated 15–20% and the direct economic burden of disease by an estimated 10%.

Materials and methods

The aim of this work is to extend the analysis to the entire world. In the following, I outline six tasks that are necessary to do so.

1. Identify major diseases for which higher serum 25(OH)D levels reduce incidence and mortality rates. As discussed in the introduction, the diseases in this category are cancer, CVD, diabetes mellitus, bacterial and viral infections, musculoskeletal diseases and neurological diseases.
2. Determine the strength of the evidence. Evidence comes in many forms. The primary epidemiological studies used to determine the effect of risk-modifying factors on disease outcome are ecological studies, case–control studies (CCS), cohort studies and cross-sectional studies. Nested case-control studies (NCCS) can be constructed from data from cohort and cross-sectional studies. Randomized controlled trials (RCTs) can also be used to test the hypotheses largely generated by the epidemiological studies. Results of individual studies can be aggregated by means of meta-analyses, thereby reducing the uncertainty of the determination. Each approach has strengths and weaknesses, as indicated in Table 2. Also, mechanisms, if they can be identified, strengthen the link between vitamin D and risk of disease. Hill (1965) outlined the criteria for causality in a biological system: strength of association, consistent findings in different populations, biological gradient, plausibility (mechanisms) and experiment (RCT). Later additions included ruling out confounding factors and bias. Reviews of the evidence with respect to Hill's criteria have been conducted for cancer (Grant, 2009c), periodontal disease (Grant and Boucher, 2010) and multiple sclerosis (MS; Hanwell and Banwell, 2011). The appropriate scientific response to a variety of research approaches is to consider them all but to carefully examine each study along with the approach, as well as compare the findings with those of other approaches.
3. Determine the serum 25(OH)D dose–mortality rate relations for each type of disease. An alternative approach would be to determine a serum 25(OH)D–all-cause mortality rate relation. This approach has at least two problems: (a) Such dose–response relations are based largely on NCCS in which a single serum draw at the time of enrollment into the cohort or cross-sectional study is used with a follow-up period that may last a decade or more. As the interval between serum draw and disease outcome increases, the value of a single measurement decreases (Grant 2011a, e-pub). (b) Such studies have been conducted largely in developed countries, where average life expectancy is >70 years and most deaths occur from cancer and CVD. In the rest of the world, average life expectancy is generally <70 years, and the fraction of deaths attributed to cancer and CVD is less.
4. Obtain mortality rates for the various regions from the tables of data for 2004 from the World Health Organization (WHO, 2008).
5. Determine population mean serum 25(OH)D levels for each region.

Table 2 Strengths and weaknesses of epidemiological studies and RCTs with respect to disease outcome related to UVB and vitamin D

Type of study	*Strengths*	*Examples*	*Weaknesses*	*Examples*
Ecological	Rapid, many cases, includes confounding factors; integration period can extend from *in utero* to death	Grant and Garland, 2006; Boscoe and Schymura, 2006; Grant and Mohr, 2009; Mohr, 2009	Some difficulty in relating UVB indices to serum 25(OH)D level	
	No factor other than vitamin D production has been proposed to explain the inverse correlation between solar UVB and cancer incidence or mortality rate			
Case–control	Serum 25(OH)D level determined at the time of diagnosis, and hence no change from baseline	Grant, 2010b; Yin *et al.*, 2010		
	Useful for dose–response relationships	Grant, 2010b		
Nested case–control	Useful for some dose–response relationships if the lag time between serum draw and disease outcome does not matter much	Grant, 2011a	After a few years, the 25(OH)D level measurement is less meaningful	Grant, 2010b; Helzlsouer, 2010; Yin *et al.*, 2010
RCT	Direct measure of the intake	Lappe *et al.*, 2007	Poor compliance Taking additional oral vitamin D	Jackson *et al.*, 2006 Urashima *et al.*, 2010
			Dose often too low	Grant and Garland, 2004; Jackson *et al.*, 2006
			Serum 25(OH)D levels generally not measured during the study; individual variations in vitamin D intake and serum 25(OH)D level	Garland *et al.*, 2011
Meta-analyses	Reduces uncertainty (95% confidence intervals)	Gandini *et al.*, 2011	Studies may not be similar (heterogeneity)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; RCT, randomized controlled trial; UVB, ultraviolet-B.

6. Calculate the mortality rate reduction for each region on the bases of death rates and dose–response relations.

This study offers a reasonable estimate based on a comprehensive reading of the journal literature. Many in positions of influence and authority regarding health policy would argue that the only reliable evidence for whether vitamin D reduces the risk of various diseases is through RCTs (IARC, 2008; Ross *et al.*, 2011). However, I believe that this restriction is unnecessary and is generally used to delay acceptance of more favorable policies for vitamin D and UV irradiance (Grant, 2009d, 2011b). Vitamin D is not a drug, for which RCTs would be required, but is instead a natural compound essential for optimal health. The tradeoff between vitamin D production and protection against the adverse effects of solar UV irradiance is what has driven changes in human skin pigmentation as humans moved out of the tropical plains (Jablonski and Chaplin, 2010). Analysis of findings from traditional epidemiological approaches should supply enough information for informed decision making. If there were a large profit to be made in selling vitamin D, the level of acceptance would be much higher.

Results and conclusions

The evidence for a beneficial role of vitamin D in reducing risk of cancer incidence and mortality rates is robust; however, several studies have not found reduced risk of cancer with respect to solar ultraviolet-B (UVB) indices, prediagnostic serum 25(OH)D level or vitamin D supplementation. As mentioned in the Materials and methods section and shown in Table 2, each approach has its strengths and weaknesses. Many papers have been published without the authors' awareness of the limitations of their studies. Thus, reviewing both the findings that support a role of vitamin D in reducing risk of cancer and those that do not is useful, as is evaluating whether the findings can be considered reliable.

Cardiovascular disease

Evidence is mounting, largely from observational studies, that vitamin D reduces the risk of CVD incidence and death

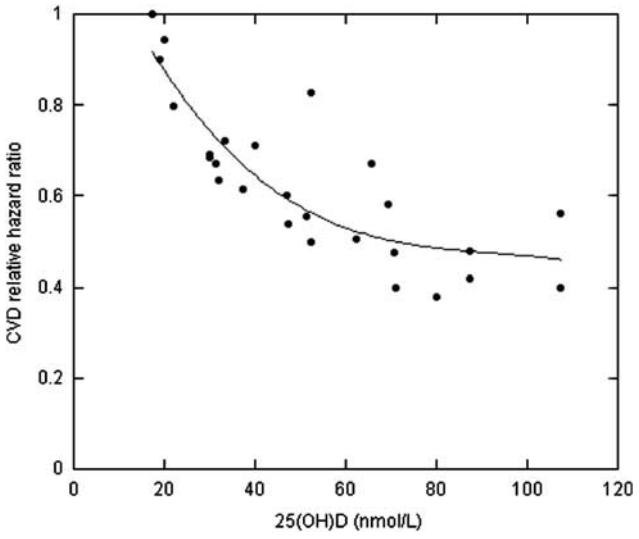

Figure 1 CVD vs 25(OH)D.

(Parker *et al*., 2010; Semba *et al*., 2010). The mechanisms seem to include reduced risk of diabetes mellitus (Parker *et al*., 2010), chronic kidney disease (LaClair *et al*., 2005), hypertension (Vaidya and Forman, 2010) and inflammation (Guillot *et al*., 2010).

Data on CVD incidence or mortality rate with respect to prediagnostic serum 25(OH)D from eight studies listed in Parker *et al*. (2010) plus a more recent report (Semba *et al*., 2010) were used in a graphical meta-analysis to determine the serum 25(OH)D level–CVD outcome. The hazard ratio (HR) for each quantile of 25(OH)D level from each study was plotted versus the mean or midpoint value for each quantile. The HR values from each study were adjusted to bring the various data sets into mutual correspondence. This approach is similar to that used for breast and colorectal cancer (Grant, 2010a). The result is shown in Figure 1. The equation for the third-order fit is:

$$HR = 1.27 - 0.0243D + 0.000255D^2 - 9.22\times10^{-7}D^3 \; r = 0.86$$

where D is 25(OH)D in nmol/l.

The HR drops by 18% with an increase in serum 25(OH)D level from 54 to 110 nmol/l.

Cancer

Ecological studies. The ecological approach was used to make the first link among solar UVB doses, vitamin D and cancer. In 1974, the brothers Cedric Garland and Frank Garland viewed the map of colon cancer mortality rates in the United States, 1950–1969, and saw that rates were lowest in the southwestern states. They knew that the Southwest was the sunniest part of the country and hypothesized that as vitamin D production was the most important physiological effect of sunlight, vitamin D must reduce the risk of colon cancer (Garland and Garland, 1980). Their group later identified breast cancer (Garland *et al*., 1990) and ovarian cancer (Lefkowitz and Garland, 1994) as vitamin D sensitive, again using the ecological approach. Prostate cancer joined the list in 1990 (Schwartz and Hulka, 1990). A new *Atlas of Cancer Mortality in the United States* was published in 1999 (Devesa *et al*., 1999). An ecological study using July 1992 solar UVB doses at the earth's surface (Leffell and Brash, 1996) raised the number of vitamin D-sensitive cancers to 15 (Grant, 2002). In the United States, solar UVB doses in summer are decidedly asymmetrical with respect to latitude and longitude: UVB doses from the Rocky Mountains to the west are similar to those ~400–700 km to the south of those east of the Rocky Mountains. This asymmetry has two causes: higher surface elevation in the west and thinner stratospheric ozone layer because of the prevailing westerly winds crossing the Rocky Mountains and pushing up the tropopause. The analysis was later extended by adding several other risk-modifying factors, such as smoking and alcohol consumption (Grant and Garland, 2006). Another group (Boscoe and Schymura, 2006) published a similar study. Ecological studies of cancer with respect to solar UVB indices have also been published for Japan (Mizoue, 2004), China (Chen *et al*., 2010), France (Grant, 2010b) and Spain (Grant, 2007a).

As not everyone accepts that solar UVB dose indices such as latitude are a reliable index of vitamin D production, an index of UVB irradiance was sought. The one adopted was incidence or death from nonmelanoma skin cancer. The most important risk factor for squamous cell carcinoma of the skin is integrated lifetime UVB irradiance, with smoking also being an important risk factor. Nonmelanoma skin cancer mortality rate by province in Spain was used in an ecological study along with latitude and lung cancer mortality rate, an index of the adverse health effects of smoking. After adjustment for smoking, 15 types of cancer had mortality rates inversely correlated with nonmelanoma skin cancer (Grant, 2007b). The types of cancer identified as vitamin D sensitive in this study had a nearly complete overlap with those identified in the United States (Grant and Garland, 2006).

Observational studies. Another common approach to investigate the role of vitamin D in the risk of cancer is the CCS or NCCS. The NCCS approach is more common, as the cases and matched control subjects can come from cohort or cross-sectional studies. CCS have nearly always found inverse correlations between serum 25(OH)D level and incidence of breast and colorectal cancer (Grant 2011a, e-pub). NCCS also find inverse correlations between serum 25(OH)D and colorectal cancer. However, for breast cancer, after a follow-up period of $\geqslant$3 years, NCCS have not found significant inverse correlations with respect to serum 25(OH)D (Grant 2011a, e-pub). The reason why long follow-up periods are not suitable for breast cancer is probably related to rapid growth of tumors after angiogenesis.

Recently, the Vitamin D Pooling Project (VDPP) found no inverse correlation between prediagnostic serum 25(OH)D and incidence of seven types of cancer (Helzlsouer, 2010). Possible reasons for why the VDPP study failed to find an inverse correlation include having too few cases (Grant, 2010c) and too long of a follow-up time (Grant 2011a, e-pub). Since the VDPP study was published, a new NCCS reported an inverse correlation between prediagnostic serum 25(OH)D and one of the VDPP cancers, ovarian cancer (Toriola *et al*., 2010).

Although observational studies have mixed findings regarding serum 25(OH)D level and cancer mortality rates, serum 25(OH)D levels at the time of diagnosis have been associated with reduced mortality rates for seven types of cancer: breast, colorectal, lung, and prostate cancers; melanoma; non-Hodgkin's lymphoma; and chronic lymphocytic leukemia (Shanafelt *et al*., 2011). This association strongly supports a role of vitamin D in reducing the risk of cancer.

One RCT used sufficient vitamin D and raised serum 25(OH)D levels enough to reduce the risk of cancer. This study was conducted on postmenopausal women living in Nebraska (Lappe *et al*., 2007). They were given 1450 mg of calcium per day, 1450 mg of calcium per day plus 1100 IU per day of vitamin D or a placebo and then monitored for 4 years. Serum 25(OH)D levels of those taking vitamin D increased from 72 to 96 nmol/l. Between the ends of the first and fourth years, those taking calcium had a 41% reduction in all-cancer incidence (not statistically significant), whereas those taking calcium plus vitamin D had a 77% reduction (statistically significant).

Respiratory infections. Respiratory infections kill 2.21 million males and 2.05 million females annually, with 98% attributed to lower respiratory infections. Seasonal influenza kills between 250 000 and 500 000 annually (WHO, 2007). Most of the remaining deaths are attributed to pneumonia, with about half of the deaths before 5 years of age, and most of the rest over the age of 60 years.

Evidence increases that vitamin D reduces the risk of incidence of and death from influenza and pneumonia. Cannell *et al.* (2006) hypothesized that epidemic influenza is largely seasonal because of the annual cycle of solar UVB and vitamin D production. Two RCTs have supported this hypothesis (Urashima *et al*., 2010 and references therein). An observational study that recommended 95 nmol/l as the serum 25(OH)D level to significantly reduce the risk (Sabetta *et al*., 2010) also supported the Cannell hypothesis.

Good evidence also exists that vitamin D reduces the risk of pneumonia. An ecological study found a significantly reduced case fatality rate from the 1918–1919 flu pandemic in the United States (Grant and Giovannucci, 2009). An RCT in Kabul found a significantly reduced incidence rate among children who took large doses of vitamin D_3 (Manaseki-Holland *et al*., 2010).

Other respiratory diseases. COPD accounts for 75% of other respiratory disease mortality rates (WHO, 2008). Several studies have reported lower serum 25(OH)D levels among those with COPD. One of the first was from Spain, reporting that those with COPD and not taking glucocorticoids had about half the serum 25(OH)D levels of control subjects (Riancho *et al*., 1987). A cross-sectional study from the United States linked serum 25(OH)D levels to lung capacity (Black and Scragg, 2005), as did an observational study of current and former smokers (Janssens *et al*., 2010). The mechanism of COPD risk reduction by vitamin D seems to include its influence on the prevalence of 'various cytokines, cellular elements, oxidative stress and protease/antiprotease levels (that) appear to affect lung fibroproliferation, remodelling and function' (Gilbert *et al*., 2009).

Tuberculosis

TB mortality rates are highest in Africa and the Western Pacific regions. Studies from these regions generally report that those who develop TB have lower serum 25(OH)D levels than those of control subjects. A study in Vietnam found that 'The prevalence of vitamin D insufficiency was 35.4% in men with TB and 19.5% in controls ($P = 0.01$). In women, there were no significant differences in serum 25(OH)D and serum (parathyroid hormone) levels between TB patients and controls' (Ho-Pham *et al*., 2010).

Those who develop TB after immigrating into higher-latitude countries also have low serum 25(OH)D levels, as in the United Kingdom (Williams *et al*., 2008). A study in Georgia found that those with active TB had low serum 25(OH)D levels, which were associated with black race and indoor lifestyle (Yamshchikov *et al*., 2010).

Vitamin D reduces TB risk by inducing cathelicidin (Liu *et al*., 2007). However, vitamin D seems to have limited benefit for treating those with TB (Davies, 2010). Vitamin D treatment for those with TB seems to be beneficial only for those with the homozygous recessive *tt* genotype of the *Taq*I vitamin D receptor (Martineau *et al*., 2011).

Diabetes mellitus, type II

Evidence is mounting that vitamin D and calcium can reduce the risk of diabetes mellitus. A Harvard study indicates that vitamin D and calcium work together to reduce the risk of diabetes mellitus, type II. Those with a combined daily intake of >1200 mg of calcium and >800 IU of vitamin D had a 33% lower risk of diabetes mellitus, type II than those with an intake of <600 mg and 400 IU of calcium and vitamin D, respectively (Pittas *et al*., 2006). A meta-analysis found that the odds ratio for diabetes mellitus, type II for low versus high quantile of serum 25(OH)D was 0.45 (95% confidence interval 0.25–0.82) (Parker *et al*., 2010).

Alzheimer's disease

Evidence that vitamin D reduces the risk of Alzheimer's disease is also increasing. One set of evidence is that several

diseases linked to low serum 25(OH)D levels often precede Alzheimer's disease. Such diseases include CVD, diabetes mellitus, depression, dental caries, osteoporosis and periodontal disease (Grant, 2009a). A second is that low vitamin D has been associated with cognitive impairment (Llewellyn *et al*., 2011), often the first sign that Alzheimer's disease is developing.

Falls and fractures
Most deaths from falls and fractures are because of accidental falls in late age. Very good evidence exists that low serum 25(OH)D levels are a risk factor for falls and fractures due to musculoskeletal diseases. Such evidence includes observational studies of serum 25(OH)D level (Cauley *et al*., 2008) and RCTs with vitamin D supplementation (Pfeifer *et al*., 2009). The reduction in risk is ~25% for higher serum 25(OH)D levels.

Meningitis
No direct evidence links low serum 25(OH)D levels to risk of meningitis. However, a reasonable amount of indirect evidence from several continents exists. In the United States, those with darker skin have increased risk (Sharip *et al*., 2006), and rates are highest in winter and lowest in summer (Kinlin *et al*., 2009; Sharip *et al*., 2006). Because meningitis is linked to bacterial infections, and vitamin D reduces the risk of bacterial infections through induction of cathelicidin and defensins (Gombart, 2009), one can reasonably expect vitamin D to reduce the risk of meningitis.

Parkinson's disease
We have modest evidence that low serum 25(OH)D level is a risk factor for Parkinson's disease. This idea was hypothesized on the basis of higher rates in northern US states (Newmark and Newmark, 2007). Perhaps the strongest evidence is from a study of outdoor work and risk of Parkinson's disease in Denmark. The odds ratio decreased consistently with respect to the amount of outdoor work, reaching a low of 0.72 (95% confidence interval 0.63–0.82) for maximal outdoor work (Kenborg *et al*., 2011).

Maternal sepsis
No studies of vitamin D and maternal sepsis seem to have taken place. However, an ecological study offers reasonable evidence that higher serum 25(OH)D level is associated with reduced risk of sepsis in the United States, on the basis of racial, seasonal and geographic variations (Grant, 2009e). The mechanism is induction of cathelicidin by vitamin D (Mookherjee *et al*., 2007).

Maternal hypertension (pre-eclampsia)
Good evidence has emerged that vitamin D reduces the risk of pre-eclampsia. An NCCS found that a 50-nmol/l decline in 25(OH)D concentration doubled the risk of pre-eclampsia (adjusted odds ratio 2.4; 95% confidence interval 1.1–5.4) (Bodnar *et al*., 2007). In a study in South Carolina, subjects with early-onset severe pre-eclampsia ($n=50$) had lower total 25(OH)D levels than those of healthy control subjects ($n=100$; $P<0.001$). This difference in total 25(OH)D remained significant after control for potential confounders (Robinson *et al*., 2010).

Multiple sclerosis
The evidence that vitamin D reduces the risk of MS is strong. The primary risk factor for MS is an adverse reaction to the Epstein–Barr virus. This reaction generally occurs in late winter or early spring, when serum 25(OH)D levels are lowest. As a result, MS prevalence increases with latitude (Grant, 2010d). A review outlined the evidence that vitamin D reduces the risk of MS (Ascherio *et al*., 2010).

A summary of the types of evidence supporting the role of solar UVB and/or vitamin D in reducing the risk of developing each disease discussed is presented in Table 3. The estimation of strength of the evidence is based on such factors as the number of studies and types of studies, and is the opinion of the author. Although RCTs are considered required to demonstrate that pharmaceutical drugs are both efficacious and not harmful, vitamin D is a natural compound with which humans have lived with forever, and hence it may not be necessary to conduct RCTs to demonstrate the protective effects of vitamin D against many types of disease.

Serum 25(OH)D levels
I adopted a value of 54 nmol/l for all regions of the world for use in this study on the basis of a meta-analysis of cross-sectional studies on global serum 25(OH)D status (Hagenau *et al*., 2009). The minimal variation with latitude found in that study is counterintuitive, but variations in skin pigmentation, time spent out of doors and clothing and oral intake of vitamin D may explain it.

Premature mortality rates attributed to low serum 25(OH)D levels
Deaths attributed to each type of disease listed in Table 1 were summed for each of the six regions. Although the evidence for the various diseases varies from preliminary to very convincing, I thought that including all these diseases in the analysis would help focus attention on all of them. Even if the evidence is not strong for some of the minor diseases, their inclusion would not significantly affect the results. In fact, adding the seven minor diseases to the six major diseases increases the percentage of deaths considered vitamin D sensitive by ~3%.

The fraction of vitamin D-sensitive diseases that could be postponed is assumed to be 20%. The HR for CVD shown in Figure 1 drops by 18% in going from 54 to 110 nmol/l. For

Table 3 Summary of evidence reported supporting the role of UVB and/or vitamin D in reducing the risk of diseases discussed in this work

Disease	*Ecological–geographical*	*Ecological–season*	*Observational*	*Cross-sectional*	*RCT*	*Strength*
Cardiovascular disease		Y	Y	Y		Strong
Cancer—bladder	Y		Y			Strong
Breast, colorectal	Y		Y	Y		Strong
Non-Hodgkin's lymphoma	Y		Y			Strong
Ovarian	Y		Y			Strong
Pancreatic	Y		X, Y			Moderate
Prostate	Y		N			Weak
12 other cancers	Y		N			Moderate
All cancer	Y		Y	Y	Y	Strong
Respiratory infections		Y	Y	Y	Y	Strong
Other respiratory diseases		Y	N	Y		Weak
Tuberculosis		Y	Y			Strong
Diabetes mellitus type 2			Y			Moderate
Alzheimer's disease			Y			Weak
Falls and fractures		Y	Y	Y	Y	Strong
Meningitis		Y				Weak
Parkinson's disease	Y		Y			Weak
Sepsis		Y	Y	Y		Moderate
Maternal hypertension		Y	Y			Moderate
Multiple sclerosis	Y	Y	Y			Strong

Abbreviations: N, null finding; RCT, randomized controlled trial; UVB, ultraviolet-B; X, contradictory finding; Y, supporting evidence.

Table 4 Estimates of reduced mortality rates for the six geopolitical regions

Region	*Sex*	*All (deaths × 1000)*	*Vitamin D (deaths × 1000)*	*RR*	*Reduced (deaths × 1000)*	*Reduced (%)*	*LE (years)*	*Increase (years)*
Africa	M	5780.1	2174.3	0.20	444.9	7.7	45	2.0
	F	5468.0	2077.5	0.20	415.5	7.6	46	2.0
Americas	M	3260.8	2162.9	0.20	432.6	13.3	65	2.0
	F	2897.4	2223.2	0.20	444.6	15.3	68	2.3
E. Mediterr.	M	2396.4	1256.3	0.20	251.3	10.5	55	1.6
	F	1909.9	1047.7	0.20	209.5	11.0	57	1.9
Europe	M	4846.7	3754.1	0.20	750.8	15.6	64	2.2
	F	4646.3	4017.8	0.20	803.6	17.3	70	2.2
Southeast Asia	M	8103.4	4615.6	0.20	923.1	11.4	56	2.1
	F	7176.0	4125.5	0.20	825.1	11.5	57	2.1
Western Pacific	M	6643.9	5068.0	0.20	1013.6	15.3	65	2.3
	F	5547.5	4446.3	0.20	889.3	16.0	68	2.3
Total	M	30 821.3	19 018.0	0.20	3803.6	12.3		
	F	27 645.1	17 887.0	0.20	3577.4	12.9		

Abbreviations: E. Mediterr., Eastern Mediterranean; F, female; LE, life expectancy; M, male; RR, risk reduction.

the same change, the odds ratio for colorectal cancer drops by 33%, whereas that for breast cancer drops by 34%, on the basis of observational studies (Grant, 2010a). Many cancers have similar geographical variations in the United States (Grant and Garland, 2006). Large reductions in the risk of respiratory infections have been noted for higher serum 25(OH)D levels (Sabetta *et al.*, 2010; Urashima *et al.*, 2010). A preliminary serum 25(OH)D dose–all-cause mortality rate relation based on observational studies is similar to those for CVD (Figure 1) and breast and colorectal cancer (Grant, 2010a). The serum 25(OH)D level–disease outcome relations are similar for disease outcomes as well as parathyroid hormone levels (Lappe *et al.*, 2006), suggesting that a single dose–response relation suffices for many, if not all, vitamin D effects.

The choice of the value of 20% reduction in mortality rates is based on considering the dose–response relations to date, degraded to some extent to account for unknown relations for several diseases, as well as not knowing at what stage of life vitamin D is most effective. Evidence from some studies indicates that the benefits of vitamin D start to accrue *in utero* and continue throughout life. Therefore, doubling serum 25(OH)D levels at the population level at a given time would result in reductions in mortality rates that would slowly increase.

The results are given in Table 4. The fraction of the death rate that could be reduced varies from 0.076 for females in Africa to 0.173 for females in Europe. The fraction is proportional to the life expectancy of each region with a slope of 0.36% per year ($r = 0.95$) for males and 0.39% per

year ($r = 0.99$) for females. Interestingly, the increased life expectancy is ~2 years regardless of life expectancy or fraction of death rate reduced: those with lower life expectancy have more years remaining at the age of life expectancy.

The results from this study are similar to those from previous studies for North America (Grant, 2009b; Grant *et al*., 2010) and Europe (Grant *et al*., 2009, 2011; Grant and Schuitemaker, 2010).

To implement policies to increase serum 25(OH)D levels at the national or regional level, government health policy-makers would have to agree that vitamin D has many health benefits and that society would benefit from higher levels. Unfortunately, such agreement is sorely lacking to date. For example, the International Agency for Research on Cancer (IARC) reviewed the evidence regarding vitamin D and cancer, finding a beneficial effect only for colorectal cancer (IARC, 2008). However, the members of the review committee were largely dermatologists and made many errors and omissions in their review (Grant, 2009d).

Gillie (2010) discussed the situation in the United Kingdom:

> Present knowledge suggests that the risk of some chronic diseases could be reduced if vitamin D intake or sun exposure of the population were increased. Yet policy and public health recommendations of the UK government and its agencies (For example, the Health Protection Agency, the Food Standards Agency) and of Cancer Research UK have failed to take full account of established and putative benefits of vitamin D and/or sunshine. The epidemic of chronic disease in the UK, which is associated with and caused at least in part by vitamin D insufficiency, has not been adequately recognized by these agencies, and too often measures taken by them have been misguided, inappropriate or ineffective.

More recently, the Institute of Medicine (IOM) of the National Academies reviewed vitamin D, concluding that the only health benefit was for the bones and that the adequate serum 25(OH)D level was 50 nmol/l, which could be achieved by oral intake of 600 IU per day for those <71 years and of 800 IU for those ⩾71 years (Ross *et al*., 2011). Unfortunately, federal sponsors directed the committee not to consider studies where vitamin D came from nonoral sources such as solar UVB irradiance and CCS that measured serum 25(OH)D levels at the time of disease diagnosis. These two types of studies provide much of the stronger evidence for several diseases. The IOM report also placed undue weight on the few studies reporting a direct correlation between serum 25(OH)D levels and disease rate. As discussed in a recent paper, most such studies are anomalous and, when combined with other similar studies, the effect disappears (Grant, 2009f). Several editorials and letters to editors have criticized the IOM report (Grant, 2011b; Heaney and Holick, 2011; Holick, 2011).

The recommendations of the IOM contrast sharply with those of a 25-member international vitamin D expert panel meeting held in Paris in November 2009 (Souberbielle *et al*., 2010). This group considered 'the best evidence available based on published literature today. In addition, where data were limited to smaller clinical trials or epidemiologic studies, the panel made expert-opinion based recommendations. …A target range of at least 75–100 nmol/l was recommended'.

Several ways exist to raise serum 25(OH)D levels at the population level. One is to increase fortification of food, including adding vitamin D to bread and other grain products (Mocanu *et al*., 2009). However, food fortification in the United States provides ~250 IU/day of vitamin D, and the requirement for those who do not make vitamin D from UVB because of skin pigmentation or lifestyle is an estimated 2000–7000 IU per day (Cannell and Hollis, 2008; Garland *et al*., 2011; Whiting *et al*., 2007). Food fortification would have to be carefully tailored to each country in terms of foods most commonly consumed and variation of amount in individual diets, along with consideration of those in the population who may not consume the typical foods. However, it would be difficult for food fortification to provide ⩾2000 IU/day per person without considerable thought and pilot programs.

A second way is to make vitamin D supplements more readily available, although many who need extra vitamin D would probably not take supplements (Whiting *et al*., 2007). A third way is to promote vitamin D production from solar (Webb and Engelsen, 2006) and artificial UVB (Moan *et al*., 2009) irradiance. As noted in a study for the United States, the adverse effects of UVB irradiance would be minimal compared with the health benefits (Grant, 2009b). No matter what combination of approaches might be undertaken in different countries, there would have to be educational campaigns to encourage compliance, as well as selective monitoring of serum 25(OH)D levels to determine the efficacy of the programs.

Conflict of interest

WB Grant receives or has received funding from the UV Foundation (McLean, VA, USA), the Sunlight Research Forum (Veldhoven, The Netherlands), Bio-Tech-Pharmacal (Fayetteville, AR, USA), the Vitamin D Council (San Luis Obispo, CA, USA) and the Danish Sunbed Federation (Middelfart, Denmark).

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