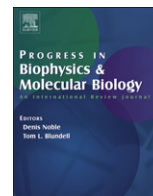




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Review

Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe

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ABSTRACT

Vitamin D has important benefits in reducing the risk of many conditions and diseases. Those diseases for which the benefits are well supported and that have large economic effects include many types of cancer, cardiovascular diseases, diabetes mellitus, several bacterial and viral infections, and autoimmune diseases such as multiple sclerosis. Europeans generally have low serum 25-hydroxyvitamin D [25(OH)D] levels owing to the high latitudes, largely indoor living, low natural dietary sources of vitamin D such as cold-water ocean fish, and lack of effective vitamin D fortification of food in most countries. Vitamin D dose–disease response relations were estimated from observational studies and randomized controlled trials. The reduction in direct plus indirect economic burden of disease was based on increasing the mean serum 25(OH)D level to 40 ng/mL, which could be achieved by a daily intake of 2000–3000 IU of vitamin D. For 2007, the reduction is estimated at €187,000 million/year. The estimated cost of 2000–3000 IU of vitamin D3/day along with ancillary costs such as education and testing might be about €10,000 million/year. Sources of vitamin D could include a combination of food fortification, supplements, and natural and artificial UVB irradiation, if properly acquired. Additional randomized controlled trials are warranted to evaluate the benefits and risks of vitamin D supplementation. However, steps to increase serum 25(OH)D levels can be implemented now based on what is already known.

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1. Introduction

Understanding of vitamin D's role in optimal health has expanded greatly in the past few years. Although vitamin D benefits were originally thought to be associated only with bone health through increasing absorption of calcium and phosphorus, several studies have extended the benefits to many noncalcemic effects. These effects include reduced risk of many forms of cancer (Garland et al., 2006; Grant, 2006a, 2009a,b), bacterial infections (Bikle, 2008), viral infections (Cannell et al., 2006), autoimmune diseases (Munger et al., 2006), and cardiovascular disease (Wang et al., 2008). Although ecological or observational studies established many of the noncalcemic health benefits, several meta-analyses and randomized controlled trials (RCTs) have provided additional evidence of the beneficial role of vitamin D, such as in reducing the risk of cancer (Lappe et al., 2007) and respiratory viral infections (Aloia and Li-Ng, 2007), and mortality rate (Autier and Gandini, 2007). Molecular and cell biology studies support a causal relationship between compromised vitamin D status and most of the aforementioned chronic diseases (Peterlik and Cross, 2005, 2006; Schwalfenberg, 2007; Holick, 2008; Ingraham et al., 2008; Palomer et al., 2008) and bacterial infections (Liu et al., 2006, 2007; Adams and Hewison, 2008; White, 2008).

Vitamin D status is usually assessed by measurements of serum 25-hydroxyvitamin D [25(OH)D]. Levels of 25(OH)D are relatively low in most European countries. Europe lies between 35° and 70°N latitude. At latitudes above 40°–45°N, generating vitamin D from solar radiation is impossible for 4–5 months of the year (Webb et al., 1988). The half-life of 25(OH)D in the body is 4–6 weeks (Heaney et al., 2003), so without supplements, food fortification, or vitamin D-rich foods such as fatty cold-water ocean fish and fish liver oil (Lu et al., 2007), serum 25(OH)D levels fall significantly in winter and early spring. Forty-five-year-old British people's 25(OH)D levels varied from 15 ng/mL in February to 30 ng/mL in September (Hypponen and Power, 2007). Other studies have also documented low serum 25(OH)D levels among those living in Europe (van der Wielen et al., 1995; Lips et al., 2001; Kudlacek et al., 2003; Zittermann et al., 2005). In a study of 7705 postmenopausal women with osteoporosis, serum 25(OH)D levels were much lower in southern Europe (20–25 ng/mL) than in northern Europe (≤ 35 ng/mL) (Lips et al., 2001). However, mean serum 25(OH)D levels in children, adolescents, and adults in Europe were between 8 and 24 ng/mL, with no trend for latitude except for Spain, where the value was 28 ng/mL (Zittermann et al., 2005). Few European countries effectively fortify foods with vitamin D (Calvo et al., 2005).

The recommended daily oral intake of vitamin D is typically 200–400 IU. This amount is primarily related to prevention of rickets (Greer, 2008). Many trials of vitamin D supplementation in the past decade have found that a level of 400 IU/day does not prevent fractures (Bischoff-Ferrari et al., 2005) or cancers (Grant

and Garland, 2004). However, daily doses of 800–2000 IU, often with 1000–1500 mg of calcium, reduced the risk of fractures (Bischoff-Ferrari et al., 2005), viral infections (Aloia and Li-Ng, 2007), and cancer (Lappe et al., 2007). The optimal serum 25(OH)D level seems to be at least 40 ng/mL (Lappe et al., 2007). These results are consistent with the large body of ecologic and epidemiological evidence suggesting the benefits of higher serum 25(OH)D levels (Garland et al., 2006; Holick, 2007; Anon., 2008; Cannell and Hollis, 2008). These trials are also consistent with some molecular and laboratory research. As a result of the rapidly expanding understanding of the benefits of vitamin D, the United States National Academy of Sciences' Institute of Medicine has assembled an ad hoc Committee on Dietary Reference Intakes for Vitamin D and Calcium for the United States and Canada with a completion date of September 2010.

This review estimates the reduction in the economic burden of disease in Europe possible if the mean serum 25(OH)D level is increased to at least 40 ng/mL, based on the scientific evidence to date. The reason Europe was chosen for this study is that considerable health benefits could be achieved with increased serum 25(OH)D levels due to the high latitudes, largely indoor lifestyle, the general lack of vitamin D-fortified food, and the difficulty in obtaining vitamin D supplements.

2. Data and methods

This study involved three primary steps: determining major diseases that are vitamin D sensitive, determining the fraction of burden that might be reduced by the suggested vitamin D level for each disease, and determining the economic burden for each disease in Europe. The study is complicated because the understanding of which diseases are vitamin D sensitive is based largely on ecological or observational studies, with few meta-analyses or RCTs of vitamin D and disease outcome on which to base estimates. Thus, this study should be considered a first step, outlining the approach and providing estimates, but not yet definitive.

2.1. Vitamin D-sensitive diseases

The determination of vitamin D-sensitive diseases was based primarily on a literature search of the National Library of Medicine's PubMed database. We reviewed four categories of investigations: ecological studies, observational studies including meta-analyses, RCTs, and reports discussing the mechanisms of how vitamin D reduces the risk of the particular disease. Each approach to determining vitamin D effects has strengths and limitations. Ecological studies are often performed first to identify a vitamin D link on the basis of an index of solar ultraviolet-B (UVB) dose such as for colon cancer (Garland and Garland, 1980). Mechanisms, if known, add to the understanding and credibility of a causal relationship.

2.2. Vitamin D dose–health benefit relations

One can determine vitamin D dose–health benefit relations for the various vitamin D-sensitive diseases from a combination of ecological, observational, meta-analyses of observational, and RCT studies from the literature. One way to use results from the literature and apply them to any particular population is to obtain the serum 25(OH)D distribution for that population at risk, shift it by the desired increase, then compare the disease rates for both distributions. Since serum 25(OH)D levels generally decline with age, serum 25(OH)D levels for the entire population may overestimate the levels for those most likely to suffer from low levels. For this study, estimates were made based on mean levels for the population, rather than distributions for the older population. Since the dose–benefit relations are still preliminary, this approach was deemed adequate.

2.3. Economic burden of diseases in Europe

We applied this analysis to northern Europe (Denmark, Finland, Iceland, Ireland, Norway, Sweden, UK), western Europe (Austria, Belgium, France, Germany, The Netherlands, Switzerland), and the more developed portion of southern Europe (Greece, Italy, Portugal, Spain)—a total of 17 countries with a 2006 population of 363 million. We sought studies and reports through PubMed and the Google search engine. We also sought supporting information, such as incidence, prevalence, and mortality rates, in addition to the economic burden. Many studies were based on data from several years ago. However, by using economic data as the fraction of health care costs and gross domestic product (GDP), we can express the values in recent Euro values. In 2007, the GDP of those 17 countries was \$16,441,000 million (about €12,050,000 million as of October 14, 2008). We also obtained data on economic burden of disease in the United States or Canada for use in estimating costs when we could not find reliable data for Europe. The economic burden estimates include both the direct costs of prevention, screening, and treatment and the indirect costs such as time lost from work, services of unpaid caregivers, and premature mortality. Direct costs generally represent 25–60% of the total economic burden of disease.

We found information on the expenditures for health in European countries in a pair of publications: one for expenditure by disease in an Organisation for Economic Co-operation and Development (OECD) publication (OECD, 2006), another for total expenditure as a function of GDP on an International Monetary Fund (IMF) website (International Monetary Fund, 2008).

3. Results

The vitamin D-sensitive diseases of most interest to Europe in terms of number of people directly affected and economic burden are autoimmune diseases, cancer, cardiovascular disease, congestive heart failure infectious diseases (both bacterial and viral, especially respiratory infections), and falls and fractures. The benefits of vitamin D for many of these diseases are generally well known. However, for some diseases, such as cardiovascular diseases and infectious diseases, the benefits have become more widely understood only recently and are still the subject of research.

Table 1 summarizes observational studies that determined a vitamin D dose–disease reduction effect. The observational studies listed include case–control, cohort, and meta-analyses of case–control studies.

Table 2 summarizes RCTs for several types of diseases. Not included are any studies that used intake levels of 400 IU/day of vitamin D. Until recently, most RCTs used only 400 IU/day and

found no beneficial effect (Grant and Garland, 2004). Only recently have studies used intake levels of 800–2000 IU/day of vitamin D.

In the following sections we present the strongest evidence regarding the beneficial role of vitamin D for diseases linked to low serum 25(OH)D. The discussions are more complete for the diseases with greater economic importance. We also discuss some minor diseases that have a vitamin D benefit, in part because the results are recent and not yet well publicized.

3.1. Cancer

Evidence that low solar UVB and vitamin D are important risk factors for many types of cancer is mounting. Several reports reviewed the evidence by the end of 2005 (Garland et al., 2006; Holick, 2006; Krickler and Armstrong, 2006). Since then, several additional ecological studies (Boscoe and Schymura, 2006; Grant and Garland, 2006), observational studies (Giovannucci et al., 2006; Pilz et al., 2008a), and an RCT (Lappe et al., 2007) have supported a beneficial role of vitamin D with respect to cancer incidence and/or mortality rates. Also, studies have determined vitamin D dose–cancer incidence response relations for breast (Garland et al., 2007; Abbas et al., 2008) and colorectal (Gorham et al., 2007) cancer. On the basis of those and an observational study (Giovannucci et al., 2006) and an RCT (Lappe et al., 2007), we conclude that vitamin D intake of 1500 IU/day can reduce the all-cancer incidence rate by 30%.

There is also mounting evidence that vitamin D increases survival for those diagnosed with cancer. Perhaps the first such report was from Norway, reporting that those diagnosed with breast, colon, or prostate cancer in summer or fall had better intermediate-term survival rates (Robsahm et al., 2004). Further studies in Norway extended this finding to Hodgkin's lymphoma (Porojnicu et al., 2005). The benefit of solar UVB for these cancers is about 15–25% over a 36-month period (Porojnicu et al., 2008b). On the basis of a study of the seasonal variation of serum 25(OH)D among 45-year-old residents of England where the mean value increased from 15 ng/mL in winter to 30 ng/mL in summer (Hypponen and Power, 2007), an extra 10 ng/mL or so at the time of cancer diagnosis seems to confer a significant benefit.

Also, two recent reports found that higher solar UVB or serum 25(OH)D level increases survival rates for those with cancer. One analyzed survival rates of up to 16 years in a cohort of individuals with colorectal cancer from the Nurses' Health Study and the Health Professionals Follow-Up Study. Participants in the highest quartile of prediagnostic serum 25(OH)D (mean = 40 ng/mL) had an adjusted hazard ratio (HR) of 0.52 (95% confidence interval [CI], 0.29–0.94) for overall mortality, compared with those in the lowest quartile (mean 25(OH)D = 16.5 ng/mL) (Ng et al., 2008). The study also found a trend toward lower mortality from colorectal cancer (HR = 0.61; 95% CI, 0.31–1.19) (Ng et al., 2008). In a study of postmenopausal Canadian women, distant disease-free survival during a period of up to 17 years was significantly worse in women with prediagnostic deficient (<20 ng/mL) vs adequate (>29 ng/mL) serum 25(OH)D levels (HR = 1.94, 95% CI, 1.16–3.24; $p = 0.02$), as was overall survival (HR = 1.73, 95% CI, 1.05–2.86; $p = 0.02$) (Goodwin et al., 2008). Other studies used such results to suggest that racial disparities in breast cancer survival rates in the United States are due to racial differences in serum 25(OH)D (Grant, 2006b, 2008a).

Incidence or death from nonmelanoma skin cancer (NMSC) offers a more direct measure of integrated lifetime solar UVB dose as an index of vitamin D production for cancer risk. Integrated lifetime UVB irradiance is the most important risk factor for squamous cell carcinoma and an important risk factor for basal cell carcinoma (Armstrong and Krickler, 2001). However, for melanoma, chronic UV irradiance can reduce the risk, but sporadic UV

Table 1
Vitamin D dose–disease response relations from observational studies.

Disease and outcome	Results with respect to serum 25(OH)D level (ratio, [95% CI])	Reference
Hip fractures	RR = 0.64 (0.46–0.89) for ≥ 25 ng/mL vs <25 ng/mL	(Looker and Mussolino, 2008)
Cancer, colorectal incidence	50% reduction for ≥ 33 ng/mL compared to ≤ 12 ng/mL	(Gorham et al., 2007)
Cancer, breast, incidence	50% reduction for 30 ng/mL vs 5 ng/mL	(Garland et al., 2007; Abbas et al., 2008)
Colorectal cancer survival	HR = 0.52 (0.29–0.94) for >40 ng/mL vs ≤ 16.5 ng/mL	(Ng et al., 2008)
Breast cancer survival	HR = 1.94 (1.16–3.24) for >29 ng/mL vs <20 ng/mL	(Goodwin et al., 2008)
Cardiovascular disease, incidence	HR = 1.80 (1.05–3.08) for <10 ng/mL vs >15 ng/mL	(Wang et al., 2008)
Coronary heart disease, incidence	RR = 2.09 (1.24–3.54; $p_{\text{trend}} = 0.02$) for <10 ng/mL vs >30 ng/mL	(Giovannucci et al., 2008)
Coronary heart disease, death	HR = 2.17 (1.58–2.99) for <10 ng/mL; HR = 1.40 (1.03–1.91) for >10 ng/mL but <20 ng/mL	(Dobnig et al., 2008)
Hypertensive disease, incidence	RR = 3.18 (1.39–7.29) for <15 ng/mL vs >30 ng/mL	(Forman et al., 2007)
Peripheral artery disease, prevalence	PR = 1.35 (1.15–1.59) for each 10 ng/mL lower	(Melamed et al., 2008b)
Diabetes mellitus, prevalence	OR = 0.25 (0.11–0.60) for non-Hispanic whites for ≥ 32.4 ng/mL vs ≤ 17.6 ng/mL	(Scragg et al., 2004)
Diabetes mellitus, incidence, males	OR = 0.28 (0.10–0.81) for >30 ng/mL vs <10 ng/mL	(Knekt et al., 2008)
Congestive heart failure, death	0.51 (0.33–0.77); 1,25(OH) ₂ D >73 pmol/L vs <43 pmol/L	(Zittermann et al., 2008)
COPD	Mean FEV1 was 126 mL (SE, 22 mL) and mean FVC was 172 mL (SE, 26 mL) greater for ≥ 34.3 ng/mL vs ≤ 16.2 ng/mL	(Black and Scragg, 2005)
Multiple sclerosis, incidence	OR = 0.59 (0.36–0.97) for 20 ng/mL increase	(Munger et al., 2006)
Multiple sclerosis, case-fatality rate	0.48 (95% CI, 0.28–0.80) for high vs low occupational UV exposure	(Westberg et al., 2009)
Mortality rate	HR = 2.08 (1.60–2.70) for median 25(OH)D = 7.6 ng/mL vs 28.4 ng/mL	(Dobnig et al., 2008)
	MRR = 1.26 (1.08–1.46) for >32.1 ng/mL vs <17.8 ng/mL	(Melamed et al., 2008a)
	HR = 2.17 (1.27–3.72; $P = 0.01$) for <20 ng/mL	(Kuroda et al., 2009)

Note: AL, attachment loss; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; HR, hazard ratio; MRR, mortality rate ratio; NHANES III, National Health and Nutrition Examination Survey III; OR, odds ratio; PR, prevalence ratio; RR, risk ratio; SE, standard error.

irradiance and sunburning are risk factor (Kennedy et al., 2003). Diagnosis of NMSC is associated with reduced risk of solid tumours (Grant, 2007a,b, 2008b; Tuohimaa et al., 2007; Soerjomataram et al., 2008). The finding of inverse correlation between NMSC and solid tumour is generally limited to latitudes equatorward of about 40°, the study in The Netherlands (Soerjomataram et al., 2008) being an exception. Solar UVB doses (Webb and Engelsens, 2006) and temperatures in The Netherlands are not high enough for people there to expose enough skin enough of the year to produce sufficient vitamin D to reduce the risk of cancer. However, studies found a beneficial effect on survival in Norway for several types of cancer related to UVB irradiance in summer or fall (Robsahm et al., 2004; Porojnicu et al., 2008b).

Reasonable evidence of a beneficial role of vitamin D exists for about 16 types of cancer (gastrointestinal: colon, esophageal, gall-bladder, gastric, pancreatic, rectal; urogenital: bladder, kidney, and prostate; female: breast, endometrial, ovarian, and vulvar cancer; and blood cancers: Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma).

Several reports have discussed the mechanisms whereby vitamin D reduces the risk of cancer. The protective effects of vitamin D result from its role as a nuclear transcription factor involved in auto-regulation of cell growth, differentiation, apoptosis, and a wide range of cellular mechanisms central to the development of cancer (Ingraham et al., 2008). Vitamin D also reduces angiogenesis around tumours (Majewski et al., 1996), reduces metastasis (Getzenberg et al., 1997), and down-regulates insulin-like growth factor-I binding proteins (Cómez, 2006). Vitamin D probably also reduces the risk of viral infection for cancers for which some viral infections appear to be a risk factor,

such as gastric, prostate, testicular, and thyroid cancer, lymphoma, and multiple myeloma (Grant, 2008b,c). The evidence for this hypothesis includes the finding that the geographical variation of mortality rates for these cancers increases with latitude in the United States, an index of wintertime solar UVB, separate from a reduced rate with respect to summertime solar UVB, which is much higher in the western United States than in the eastern United States at any given latitude (Lefell and Brash, 1996). This scenario exists because of the higher surface elevation in most of the West and the thinner stratospheric ozone layer in the West because of the prevailing westerly winds that raise the tropopause when they push air over the Rocky Mountains. Studies have also reported viral DNA in solid tumours for these cancers or a seasonal variation of incidence rate for lymphomas related to solar UVB (Chang et al., 2005; Koutros et al., 2007).

3.2. Cardiovascular diseases

Several articles this year reported observational studies of serum 25(OH)D levels with respect to cardiovascular disease incidence or death (Dobnig et al., 2008; Pilz et al., 2008a; Wang et al., 2008).

Several mechanisms might explain the benefit of vitamin D in reducing the risk of cardiovascular disease. Vitamin D acts on the renin–angiotensin system (Li et al., 2004). Vitamin D reduces the risk of type 2 diabetes mellitus, an important risk factor for cardiovascular disease (O'Keefe et al., 2008), through regulation of plasma calcium levels, which regulate insulin synthesis and secretion, and through a direct action on pancreatic β -cell function (Reis et al., 2005; Palomer et al., 2008). Vitamin D reduces the risk of bacterial and viral infections (Aloia and Li-Ng, 2007; Bikle, 2008;

Table 2
Results of RCTs of vitamin D for disease prevention.

Disease and outcome	Results with respect to vitamin D supplementation (ratio [95% CI])	Reference
Type 1 diabetes mellitus incidence, infants	RR = 0.22 (0.05–0.89) for 2000 IU/day vs no supplementation	(Hypponen et al., 2001)
Hip fracture	RR = 0.74 (0.61–0.88) for 700–800 IU/day (no effect for 400 IU/day)	(Bischoff-Ferrari et al., 2005)
All-cancer incidence, postmenopausal women	RR = 0.65 for 1100 IU/day	(Lappe et al., 2007)
Seasonal influenza, common cold, postmenopausal black women	RR = 0.4 for 800 IU/day, 0.1 for 2000 IU/day	(Aloia and Li-Ng, 2007)
Mortality rate, meta-analysis	ReR = 0.93 (0.87–0.99) for 528 IU/day, 5.7-year observation period	(Autier and Gandini, 2007)

Note: OR, odds ratio; RR, risk ratio; ReR, relative risk.

Cannell et al., 2006; Liu et al., 2006). Bacterial and viral infections can take part in the development of atherosclerosis and trigger the occurrence of acute myocardial infarction (Rupprecht et al., 2001; Espinola-Klein et al., 2002; Guan et al., 2008; Harskamp and van Ginkel, 2008).

3.3. Diabetes mellitus

Studies have found good observational evidence that low serum 25(OH)D is a risk factor for type 2 diabetes mellitus (Knekt et al., 2008; Pittas et al., 2006, 2007). Also, the mechanisms whereby vitamin D can reduce the risk of diabetes are thought to be known (Palomer et al., 2008; Reis et al., 2005).

Observational and ecological evidence indicates that vitamin D in infancy reduces the risk of type 1 diabetes (Hypponen et al., 2001; Mohr et al., 2008; Zipitis and Akobeng, 2008). Dahlquist et al. (1999) associated two factors related to low serum 25(OH)D, maternal preeclampsia (Bodnar et al., 2007) and neonatal respiratory disease (Grant, 2008d), with risk of developing type 1 diabetes mellitus (Dahlquist et al., 1999).

3.4. Infectious diseases

For infectious and autoimmune diseases, production of human cathelicidin, LL-37, is the predominant innate immune mechanism of vitamin D. LL-37 has powerful antimicrobial activity and potent antiendotoxic activity (Mookherjee et al., 2007), and several previous reports reviewed its ability to fight infections (Adams and Hewison, 2008; Bikle, 2008; White, 2008). Most of the results to date are for bacteria, such as *Mycobacterium tuberculosis*, for which a toll-like receptor triggering of a vitamin D-mediated human antimicrobial response was identified (Liu et al., 2006). In addition, 1,25(OH)D inhibits matrix metalloproteinases (Cousens et al., 2009). In the first half of the twentieth century, those with tuberculosis were often successfully treated with solar radiation (Rollier, 1952). However, the seasonality of such viral diseases as influenza strongly suggests a beneficial effect of solar UVB and vitamin D (Cannell et al., 2006), a hypothesis that an RCT (Aloia and Li-Ng, 2007) supported.

One important benefit of vitamin D and LL-37 seems to be reduced risk of Epstein–Barr virus (EBV) infection. EBV is an important risk factor for several diseases, including Burkitt's lymphoma (Burkitt, 1983), Hodgkin's and non-Hodgkin's lymphoma and oropharyngeal cancer (Goldacre et al., 2008), infectious mononucleosis (McAulay et al., 2007), and multiple sclerosis (MS) (Ascherio and Munger, 2007). The conclusion that vitamin D reduces the risk of EBV infection comes in part from epidemiological studies of the geographical and seasonal variation in risk of diseases linked to EBV infection. It has been known for decades that the prevalence of MS increases with latitude, except for the Nordic Countries and Japan (Kurtzke, 1980). In the United States, the prevalence of MS for veterans of World War II and the Korean conflict increased strongly with latitude (Grant and Holick, 2005; Wallin et al., 2004). Diseases linked to EBV have a peak incidence rate in late winter or early spring: infectious mononucleosis (Douglas et al., 1996), Hodgkin's lymphoma (Douglas et al., 1996), and non-Hodgkin's lymphoma (Koutros et al., 2007). The strong correlation of MS prevalence with increasing latitude, but not July UVB, in the United States (Wallin et al., 2004; Grant and Holick, 2005) is further evidence that risk of MS is highest in winter.

3.5. Other vitamin D-sensitive diseases

One disease not discussed in detail but considered linked to low serum 25(OH)D is congestive heart failure. There are a number of

observational studies that found a link (Barnett et al., 2008; Kim et al., 2008; Pilz et al., 2008b; Zittermann et al., 2008).

There are additional diseases for which preliminary ecological or observational studies have linked to low serum 25(OH)D but which have not yet had the further studies that would solidify the link. Such diseases include periodontal disease (Dietrich et al., 2004), septicemia (Mookherjee et al., 2007; Grant, 2009c), asthma (Ginde et al., 2009), risk of cesarean section (Merewood et al., 2009), cognitive impairment (Buell and Dawson-Hughes, 2008; Llewellyn et al., 2009) and dementia (Grant, in press). These diseases are not included in the analyses, but could increase the benefit of increased intake and production of vitamin D.

3.6. Beneficial effects for vitamin D-sensitive diseases

Table 3 presents estimates of the beneficial effects of vitamin D for the vitamin D-sensitive diseases of most importance to Europeans. The adopted values also assume an adequate calcium intake from diet or supplements (Peterlik and Cross, 2005; Lappe et al., 2007; Holick, 2008). The expected benefit of vitamin D is reduction in risk of disease by 15–30% for diseases that have been studied.

3.7. Economic burdens of disease

Table 3 also describes the economic burdens of disease as estimated primarily from studies in Europe (but also some from the United States and Canada). The estimates include both direct medical costs and indirect costs, such as the effects of morbidity and mortality and unpaid services of caregivers. For influenza, the indirect economic burden could be five to 10 times that of the direct medical costs (Szucs et al., 2001).

According to the OECD, the mean direct expenditure for health among European members of the OECD in 2004 was $9.3\% \pm 1.2\%$ of gross domestic product (GDP). The GDP of these countries in 2007 was US\$16,441,000 million (€12,050,000 million in 2007 as of Oct. 14, 2008). Thus, if we assume the same fraction for health care expenditures in 2007, the mean direct expenditure for health care in these countries was €1,120,000 million \pm €140,000 million. Raising serum 25(OH)D levels of all Europeans to 40 ng/mL would reduce the total direct economic burden of disease by 11.4%, or €105,000 million, and would reduce the indirect economic burden of disease by €82,000 million, for a total reduction in economic burden of disease by 17.7%, or €187,000 million. The uncertainty is about 30% for the economic burden of disease and perhaps 20% for the vitamin D benefit, for a total uncertainty of approximately 40–50%. For example, meta-analyses of vitamin D dose–cancer response (Garland et al., 2007; Gorham et al., 2007) suggest that the health benefits of vitamin D would continue to increase in a nearly linear manner at least up to 60 ng/mL.

4. Discussion

4.1. Overall effect of increased serum 25(OH)D levels

One can estimate the effect of having all Europeans reach the 40-ng/mL 25(OH)D level as the product of the economic burden of each disease and the fraction of the burden that daily intake of 2000–3000 IU of vitamin D3 could reduce for some diseases (Table 3), leading to reduced mortality rates and longer healthy life expectancy.

The estimated benefits of raising the mean serum 25(OH)D of Europeans to 40 ng/mL would take many years to fully phase in across all populations. Some diseases exist for which vitamin D reduces the risk, but once they develop, the beneficial effect of vitamin D does not eliminate the disease. Some of these diseases

Table 3

Diseases related to vitamin D with average values for northern and western Europe, perhaps southern Europe.

Disease	Portion of direct health care costs (%)	Indirect costs ^a (%)	Ref.	Total (%)	Vitamin D fraction	Vitamin D cost savings ^a (%)
Osteoporosis, fractures, falls	1.5	0.5	A	2.0	0.25	0.5
Cancer	6.4	9.6 (FB)	B	16.0	0.3	4.8
Cardiovascular disease	12	6 FB; 8 Liu	C	20	0.2	4.0
Type 2 diabetes	7.0	2.4 FB	D	9.4	0.2	1.9
Congestive heart failure	1.5	0.5	E	2	0.25	0.5
Infectious diseases						
Influenza	2.5	5.0	F	7.5	0.3	2.3
Pneumonia	2.5	1.0	G	3.5	0.3	1.1
Other respiratory infections (asthma, COPD)	2.0	0.5	H	2.5	0.2	0.5
Autoimmune diseases						
Multiple sclerosis	1	0.2	I	1.2	0.5	0.6
Total	35.9	27.8		63.7		16.7

A. (Koeck et al., 2001; Grant et al., 2005; Lippuner et al., 2005).

B. (Stark, 2006).

C. (Liu et al., 2002; Leal et al., 2006).

D. (Oliva et al., 2004; Koster et al., 2006).

E. (Bundkirchen and Schwinger, 2004).

F. (Szucs et al., 2001; Ryan et al., 2006).

G. (Monge et al., 2001).

H. (Monge et al., 2001; Sennhauser et al., 2005).

I. (Kobelt et al., 2006).

^a As portion of direct health care costs; indirect costs include informal health care and loss of productivity through morbidity or mortality; FB, National Institutes of Health, National Heart, Lung and Blood Institute, Fact Book Fiscal Year 2008.

are linked to viral infections in childhood or youth, such as autoimmune diseases and some types of cancer.

While not estimated in this work, mortality rates would be reduced by 10–20%, based on several studies listed in Tables 1 and 2. That would increase life expectancy by about 2–3 years.

A related work estimated that raising mean serum 25(OH)D levels to 40 ng/mL in Canada would reduce the total economic burden of chronic diseases by 16.8% (Grant, in preparation). However, chronic diseases account for a fraction of health expenses, and the indirect costs of disease due to productivity losses in Canada were 2.3 times direct costs for cancer and 1.7 times direct costs for CVD (Policy Research Division, S. P. D., 2007).

4.2. Limitations of estimates

Factors other than solar UVB could affect ecological study results; however, many ecological studies on cancer consider other risk-modifying factors (Grant and Garland, 2006). Lifestyle and calcium intake could affect observational studies, but again, the models include many such factors (Giovannucci et al., 2006). Meta-analyses of observational studies increase the reliability of the estimated dose–response relations (Garland et al., 2007; Gorham et al., 2007). RCTs, if based on one study with a few cases, may be limited to the specific group of people and conditions involved. For this study, the values adopted are generally less than those determined from the various studies because of the inherent uncertainties in the values found in those studies.

4.3. Adverse effects of vitamin D supplementation

Another consideration is possible adverse effects from vitamin D supplementation. The most comprehensive risk assessment for vitamin D was published recently (Hathcock et al., 2007). The primary concern is the risk of hypercalcemia. The toxic signs of hypercalcemia include pain, conjunctivitis, anorexia, fever, chills, thirst, vomiting, and weight loss. However, most cases of vitamin D toxicity occurred at serum 25(OH)D levels >250 ng/mL. There has been concern that higher vitamin D levels might lead to formation of kidney stones (nephrolithiasis). However, the male health

professionals' cohort study of dietary factors found that vitamin C was a risk factor, but not vitamin D (Taylor et al., 2004).

Persons with sarcoidosis or granulomatous disease (Hewison et al., 2007), or another condition that causes high blood calcium levels should not take vitamin D supplements. In such cases, additional 1,25(OH)2D3 is produced at disease sites in close contact with serum and thus increases levels in the serum, which can increase the risk of hypercalcemia (Sharma, 2000; Hewison et al., 2007). Also, about 10–20% of those with lymphoma may experience a similar effect (Hewison et al., 2003).

Since there are few studies of long-term vitamin D supplementation at higher doses in large groups, there is still uncertainty as to the type and extent of adverse effects that might be encountered (Davis, 2008). However, since vitamin D3 supplements are bioidentical to vitamin D produced from UVB irradiance, and since 10,000–20,000 IU/day of vitamin D can be produced with whole-body UVB irradiance, it is unlikely that there will be a significant fraction of the population that would suffer adverse effects other than those with diseases known to have problems.

4.4. Roles of environment and genetics

Individual's responses to vitamin D may depend on personal genetics. For example, dietary factors and smoking may explain 70% of cancer risk in the United States (Doll and Peto, 1981). Polymorphisms of vitamin D receptor alleles affect the action of vitamin D for cancer (Davis, 2008; Thorne and Campbell, 2008) and autoimmune diseases (Bouillon et al., 2008; Ponsonby et al., 2008). Many of the cancers for which diet and smoking are risk factors are also vitamin D sensitive (Grant and Garland, 2006), thus providing an additional way to counter the effects of environment and genetics.

4.5. Sources of vitamin D

One can obtain vitamin D3 from diet, supplements, and natural and artificial UVB. Because few countries in Europe fortify food with vitamin D, cold-water ocean fish is the primary dietary source of dietary vitamin D. Given the benefits of and apparently limited

risks of vitamin D, European countries should strongly consider fortifying dairy and grain products (Natri et al., 2006). However, in the United States, where milk is fortified, the average intake from food is only 200 IU/day (Whiting et al., 2007). Solar UVB is not strong enough to generate vitamin D in the skin in most European countries in winter but can be a good source in summer (Hypponen and Power, 2007; Porojnicu et al., 2008b).

Sunbeds, which in Europe have UV output similar to that of the Mediterranean midday sun but less UVB, can also generate vitamin D. A recent investigation in Norway showed that suberythemal sunbed doses given twice per week for 5 weeks in the winter produced summertime 25(OH)D levels (Porojnicu et al., 2008a). A young individual can generate about 10,000–20,000 IU/day of vitamin D (Adams et al., 1982). Persons who use artificial UVB to tan in the United States have higher serum 25(OH)D levels than those who do not (Tangpricha et al., 2004). While both solar and artificial UV entail the risk of skin cancer, the benefits of chronic but moderate UVB irradiance outweigh the health risks except, perhaps, for those with type 1 Fitzpatrick skin type, who are at increased risk for melanoma (Raimondi et al., 2008). For example, those who develop NMSC in sunny countries (generally equatorward of 30–35° latitude) have reduced risk of most types of cancer other than lung cancer (Grant, 2007a,b, 2008b; Tuohimaa et al., 2007). Also, early-life UV irradiance is associated with reduced risk of MS (van der Mei et al., 2003) and prostate cancer (John et al., 2007). While the European Commission's Scientific Committee on Consumer Products has warned against use of sunbeds (European Commission, 2006), it based its opinion on risk factors without any consideration for benefits.

It appears that cod liver oil may not be a good source of vitamin D now since many forms of cod liver oil sold in the market have too much vitamin A (retinoic acid) (Cannell et al., 2008). The problem with higher intakes of vitamin A is that vitamin A antagonizes the action of vitamin D and its active metabolite.

Vitamin D is fat soluble and has a half-life in the body of 4–6 weeks (Heaney et al., 2003). Vitamin D can accumulate in the body, where it is stored in the adipose tissues and paid out slowly, so that higher doses of vitamin D lead to a long residence time (Rose-nstreich et al., 1971). However, with high doses (50,000 IU/day), the half-life can increase to 90 days (Wu et al., 2003).

The cost of vitamin D supplements, on the basis of retail costs over the Internet in the United States for 3000 IU/day (\$10/year), is for 364 million people, €3000 million. However, education, distribution, and testing would incur further costs, so the total cost of a vitamin D supplementation program might be as much as €10,000 million. Thus, the estimated benefit–cost ratio of a vitamin D supplementation program for Europe is nearly 20 to 1.

5. Summary and conclusion

This study indicates that increasing Europeans' serum 25(OH)D levels to at least 40 ng/mL all year could significantly reduce rates and economic burdens of several types of diseases. In most European countries, the 25(OH)D levels are typically 15–20 ng/mL below this goal. The most important benefits would come for cancer, cardiovascular disease, diabetes mellitus, respiratory infections, and dental/periodontal diseases. Although this study is based on a review of the scientific evidence to date and not on RCTs of vitamin D supplementation, as would be required for pharmaceutical drugs, the fact that solar UVB and vitamin D have coexisted with humans since our emergence as a species means that there is ample evidence by which to evaluate the benefits and risks. Given that the benefits of higher serum 25(OH)D are large and the risks are minimal, one can conclude that there is much more to gain than

to lose by moving forward to implement a new vitamin D policy soon.

Food fortification has led to health benefits. Fortification of grain products with folic acid in Canada and the United States seems to be responsible for reduced risk of stroke (Yang et al., 2006) and birth with spina bifida (De Wals et al., 2008) and, likely, colon cancer (Bentley et al., 2008). A recent economic analysis of folic acid fortification in the United States estimated \$3600 million/year saved by increasing the fortification level from 140 µg/100 g of enriched grain to 700 µg/100 g (Bentley et al., 2008).

Taken together, our findings indicate that it would be beneficial for the health ministries of European countries to familiarize themselves with the health benefits of vitamin D. There is a need not only for systems for achieving adequate vitamin D repletion and include the need for ensuring that the public and health care staff are adequately educated on the policy and on possible side effects that should be reported and also the need for the availability of rapid assessment of any possible adverse effects.

The conclusions of this paper are based primarily on ecological and observational studies. Many of the findings have been repeated in several different populations. Nonetheless, widespread acceptance of the health benefit of higher serum 25(OH)D levels would be greatly facilitated by multi-center randomized controlled trials.

Disclosure

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