HB

39

<TARGET><BILL>HB 39</BILL><SUBJECT>HB
39</SUBJECT><COMM>HFIN29</COMM></TARGET>

Alaska State Legislature

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REPRESENTATIVE PAUL SEATON
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Sponsor Statement

HB 39

HB 39 requires the Commissioner of the Department of Administration to implement procedures for decreasing the incidence of disease in Alaska in order to hold the inflation of healthcare costs of active and retired Alaska state employees to 2% per year.

According to the Institute of Social and Economic Research, total health care spending in Alaska topped $7.5 billion in Alaska in 2010, with state government employers paying over $1.6 billion. A major component of our $12 billion unfunded pension liability is retiree healthcare costs. HB 39 requires the Commissioner of Administration to put in place programs that will decrease the incidence of disease in State of Alaska employees, both current and retired, in order to hold the inflation of costs to 2% per year.

This bill focuses on preventing the incidence of disease as opposed to merely treating disease. Prevention of disease is the policy approach unanimously requested of the Governor by the legislature through HCR 5 in 2011. This is an area of healthcare where the most economic impact can be achieved. For instance, recent studies show that an action as simple as taking a daily supplement of 5,000 IU of vitamin D can dramatically reduce the risk of heart disease, diabetes, cancer, autism, gingivitis, and many other conditions.

HB 39 creates an Advisory Committee on Wellness which is charged with making recommendations to the Commissioner of Administration on ways to decrease the incidence of disease in Alaska. HB 39 will enforce a paradigm shift for the Department of Administration and the Department of Health and Social Services. It will require the agencies to implement policies to keep Alaska state employees healthy by preventing disease, rather than the common, reactive policy of waiting until people get sick and then treating them.

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House Bill 39

Sectional

Section 1

This section includes legislative findings and intent language which states that we can prevent disease by lowering the incidence of disease, and that preventing disease will slow the rate of health care cost to the State.

Section 2

This section requires the Department of Administration, to the extent legally and reasonably practicable, to implement the recommendations of the Advisory Committee on Wellness and reduce the escalation of health care costs. This section of statute applies to state life and health insurance plans.

Section 3

This section requires the Department of Administration, to the extent legally and reasonably practicable, to implement the recommendations of the Advisory Committee on Wellness and reduce the escalation of health care costs. This section of statute applies to self-insurance and excess loss insurance.

Section 4

This section establishes the Advisory Committee on Wellness in the Department of Administration, outlines the appointment and roles of committee members, and requires the commissioner of administration to respond to the committee within six months. The committee and the commissioner are required to provide copies of their recommendations and reports to the legislature and the governor on or before the second Monday in December of each year.

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Explanation of Changes

Version A to Version H

Version H of House Bill 39 adds two new subsections, (g) and (h), to section 4 of the bill. These were added to ensure the Advisory Committee on Wellness and the Department of Administration report their efforts to the legislature.

Subsection (g), page 3 lines 23-27, requires the commissioner of administration to deliver to the legislature and the governor a copy of any reports made under (f) of this bill on or before the second Monday in December of each year.

Subsection (h), page 3 lines 28-31, requires the committee to deliver to the legislature and the governor a report containing the recommendations made under (e) of this bill on or before the second Monday in December of each year.

Distributed by Rep. Paul Seaton

Dr. Cannell on vitamin D for the treatment of depression

Posted on January 15, 2015 by John Cannell, MD

Sometimes we miss an important paper. This was the case with Professor Simon Spedding's 2014 meta-analysis of randomized controlled trials (RCT) that used vitamin D to treat depression; Professor Spedding is at the University of South Australia.

Depression is a terrible disease. To a person suffering from depression, sometimes it seems like life is not worth living. It is the leading cause of disability in the U.S. As a psychiatrist, I can tell you that many times conventional antidepressants do not work and patients are left hanging in "partial remission," which means their depression has improved but is still present.

There is a controversy raging within the academic field of psychiatry; some are claiming that certain RCTs used by pharmaceutical companies to get FDA approval of antidepressants were flawed and that antidepressants are no better than placebo when it comes to treating depression.

In his analysis of the effects of vitamin D supplementation on depression, Dr. Spedding excluded RCTs that had "biological flaws." Professor Robert Heaney first described the concept of biological flaws in studies of nutrients. In Dr. Spedding's review, biologically flawed scientific studies included RCTs with one of the following:

Inappropriate interventions (interventions that did not include vitamin D).
Interventions producing the opposite effect of that intended (interventions that included Vitamin D, but reduced the 25OHD level in the intervention group).
Ineffective interventions that did not improve vitamin D status (did not significantly change the 25OHD level).
Where the baseline 25OHD level was not measured in the majority of participants.
Where the baseline 25OHD level indicated sufficiency (not deficiency) at baseline.

I'd like to add one more criterion which well-designed RCTs should uphold: the RCT must include subjects with the condition being studied. For example, researchers should not conduct a RCT of vitamin D in non-depressed subjects to see if vitamin D has a treatment effect on depression or overall mood.

Dr. Spedding found that 8 of the 15 extant RCTs had biological flaws. Of the 7 RCTs without flaws, 6 RCTs found that vitamin D significantly improved depression.

Dr. Spedding concluded:

"The effect size for Vitamin D in depression demonstrated in this meta-analysis is comparable with the effect of anti-depressant medication, an accepted treatment for depression. Should

these results be verified by future research, these findings may have important clinical and public health implications."

I treat a lot of patients with major depression. When I begin treatment, I place them all on 50,000 IU/day of vitamin D3 for two weeks and then place them on a maintenance dose of 10,000 IU/day. I wish I could tell you that vitamin D is a panacea for depression; it is not. It certainly helps some patients but most patients require treatment with conventional medication as well, and even then, some of those do not achieve full remission of their depression.

Source

Spedding S.Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. Nutrients. 2014 Apr 11;6(4):1501-18. doi: 10.3390/nu6041501. Review.

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Review

Vitamin D and Depression: A Systematic Review and Meta-Analysis Comparing Studies with and without Biological Flaws

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Abstract: Efficacy of Vitamin D supplements in depression is controversial, awaiting further literature analysis. Biological flaws in primary studies is a possible reason meta-analyses of Vitamin D have failed to demonstrate efficacy. This systematic review and meta-analysis of Vitamin D and depression compared studies with and without biological flaws. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The literature search was undertaken through four databases for randomized controlled trials (RCTs). Studies were critically appraised for methodological quality and biological flaws, in relation to the hypothesis and study design. Meta-analyses were performed for studies according to the presence of biological flaws. The 15 RCTs identified provide a more comprehensive evidence-base than previous systematic reviews; methodological quality of studies was generally good and methodology was diverse. A meta-analysis of all studies without flaws demonstrated a statistically significant improvement in depression with Vitamin D supplements (+0.78 CI +0.24, +1.27). Studies with biological flaws were mainly inconclusive, with the meta-analysis demonstrating a statistically significant worsening in depression by taking Vitamin D supplements (−1.1 CI −0.7, −1.5). Vitamin D supplementation (≥800 I.U. daily) was somewhat favorable in the management of depression in studies that demonstrate a change in vitamin levels, and the effect size was comparable to that of anti-depressant medication.

Keywords: Vitamin D supplementation; depression; biological plausibility; meta-analysis; systematic review; 25OHD

1. Introduction

Depression affects 350 million people worldwide, is the leading cause of disability and the fourth-leading cause of the global disease burden [1]. However, the effectiveness of conventional treatments for depression is questioned: meta-analyses of drug treatments demonstrate minimal difference from placebo, comparisons of real and sham electroconvulsive therapy show little difference after a month, and the evidence for the use of specific cognitive interventions is weak [2]. Therefore we examined the evidence for other approaches to the management of depression.

The association between depressive disorders and Vitamin D deficiency from a lack of sun exposure is well established and was first noted two thousand years ago [3], therefore we considered the evidence for the effectiveness of Vitamin D supplementation.

Vitamin D is a unique secosteroid hormone formed mainly by photosynthesis, so an indoor lifestyle and sun-avoidance leads to deficiency (25OHD <50 nmol/L) [4]. Vitamin D deficiency is now a global public health problem affecting a billion people worldwide [5]. Even in sunny Australia, deficiency affects one third of the population [6], with much higher rates observed in migrant populations [7,8]. There has been an increase in the prevalence of Vitamin D deficiency [9] and a ten-fold increase in spending on supplements in the US over the last decade [10].

Knowledge of Vitamin D has grown exponentially [11] and 95% of our current knowledge was published in the last 15 years [12]. This demonstrates new mechanisms and diseases associated with deficiency including cancer, cardiovascular disease, diabetes, and premature mortality [4]. Whilst Vitamin D was believed to follow Funk's model of vitamins, having a single mechanism and function limited to calcium and bone metabolism [13], the mechanisms of action of Vitamin D are now recognized to be endocrine, paracrine and autocrine via Vitamin D receptors (VDRs) [14] affecting most physiological systems, including the brain [15]. The enzymes necessary for the hydroxylation of 25hydroxyvitamin D (25OHD) to the active form 1,25dihydroxyvitamin D are present in the hypothalamus, cerebellum, and substantia nigra [16]. Vitamin D modulates the hypothalamic-pituitary-adrenal axis, regulating adrenalin, noradrenaline and dopamine production through VDRs in the adrenal cortex [17]; and protects against the depletion of dopamine and serotonin centrally [18]. Therefore, biological plausibility for the action of Vitamin D in depression has been established.

Epidemiological evidence shows that Vitamin D deficiency is associated with an 8%–14% increase in depression [19–22] and a 50% increase in suicide [23]; however, causality and efficacy of supplementation remain controversial [10,24] awaiting confirmation by systematic review and meta-analysis.

Four systematic reviews of Vitamin D efficacy in depression, but no meta-analysis, have been published [25–28]. These reviews provide conflicting results due to the limited number of studies found and the inclusion of inappropriate studies. Based on six RCTs deemed relevant, the Institute of Medicine (IOM) [25] concluded there was "inconclusive evidence of an effect" although four of these RCTs showed a beneficial effect of Vitamin D supplementation in depression. The inclusion of the other two studies [29,30] described by the IOM as "RCTs of Vitamin D" was inappropriate as; one used calcium and not Vitamin D as the intervention, and the other was not an RCT in the opinion of

the study authors as the intervention decreased 25OHD levels. Similarly, consistent conclusions could not be drawn from the other systematic reviews [26–28], as these found so few of the primary studies.

These reviews mirror the inconsistent results found across Vitamin D research as demonstrated by the twenty four conflicting meta-analyses for falls, fractures, and all-cause mortality [31]. The reason Vitamin D meta-analyses fail to produce useful results is thought to be biological flaws in primary studies. These flaws lead to null results [32] as the intervention does not change the Vitamin D status however these flaws may be overlooked when evaluating the research for Vitamin D and other nutrients [33,34].

The concept of "biological flaws" arises from the work of Heaney and others [33,34], and refers to limitations in the design of primary studies which preclude them from testing the research hypothesis. The hypothesis being addressed in this review is that rectifying Vitamin D deficiency decreases depressive symptoms. However some trials have limitations in their study design that prevent this evaluation. This hypothesis can only be tested if participants are Vitamin D deficient at baseline and then receive a large enough dose of Vitamin D supplements to achieve Vitamin D sufficiency during the trial. Vitamin D deficiency cannot be demonstrated if the level of 25OHD is sufficient or higher or not tested at baseline. An ineffective dose of Vitamin D is one that would not be expected to increase the level of 25OHD from deficient to sufficient.

Trials with these biological flaws may demonstrate the limitations of the study design rather than the effectiveness of Vitamin D supplements for changing health outcomes. The parallel in pharmaceutical research to these nutrient studies with biological flaws would be trialling a drug known to be ineffective or on patients already taking a full dose of the drug. Thus biological flaws are a critical element that differentiates nutrient research from pharmaceutical research.

This review was designed to estimate the effect of Vitamin D supplementation in depression and examine the influence of biological flaws in primary studies on the meta-analyses.

2. Methods

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, systematically identifying and appraising peer-reviewed RCTs reporting on the effect of Vitamin D supplementation for individuals with symptoms of depression with the objectives of investigating:

- the primary evidence for Vitamin D supplementation and depression from RCTs;
- the types of subjects, the dose of Vitamin D supplementation, the control interventions and the measures of outcome used;
- methodological quality of the studies;
- biological flaws in the study design, and
- estimates of the size of the effect.

2.1. Search Approach

A systematic search for relevant RCTs was performed evaluating oral Vitamin D supplementation that included data on depression using four library databases of PsychINFO, MedLine, PubMed and Cochrane online library. Search approaches for the different databases can be obtained from the researchers. All databases were searched from inception to October 2012, with eligible papers limited to English language and human subjects.

2.2. Independence

Two independent researchers investigated the library databases to reduce errors/bias in accessing evidence. The reference lists of four systematic reviews [25–28] were hand-searched to identify other RCTs.

2.3. Eligible Studies

RCTs were included where the intervention was Vitamin D supplementation and excluded where trials were not RCTs or used surrogate interventions. Studies were not excluded on their methodological quality as the entire evidence base was required to address the aims of this research.

2.4. Decision-Making

Relevant publications were identified from title, abstract and study descriptors by one researcher; the decision to include was independently validated by a second and disagreements were referred to third for an independent ruling.

2.5. Critical Appraisal

Methodological quality of articles was critically appraised with PEDro [35]. Trials were rated with a checklist, the PEDro scale. This considers two aspects of trial quality; internal validity of the trial and whether the trial contains sufficient statistical information to make it interpretable. It does not rate external validity or the effect size.

2.6. Data Extraction

Data was extracted for participants, 25OHD levels, study timeframes, interventions, outcome measures, measures of effect, methodological quality scores, and biological flaws.

2.7. Biological Flaws

Biological flaws in primary studies were identified. These studies included:

- inappropriate interventions (interventions that did not include Vitamin D), or
- interventions producing the opposite effect of that intended (interventions that included Vitamin D, but reduced the 25OHD level in the intervention group), or

- ineffective interventions that did not improving Vitamin D status (did not significantly change the 25OHD level), or
- where the baseline 25OHD level was not measured in the majority of participants, or
- where the baseline 25OHD level indicated sufficiency (not deficiency) at baseline.

Studies were grouped according to the presence of biological flaws, and compared by date of publication, methodological quality, outcome measure, and study outcome.

2.8. Meta-Analysis

Meta-analyses were performed using MedCalc where data was available on diagnosis, dose, outcome measure, and biological flaws. Estimates of the size of effect using the standardised mean difference (SMD) were compared according to the presence of biological flaws in primary studies.

For meta-analysis of studies with a continuous measure, MedCalc uses the "Hedges g" statistic as a formulation for the SMD under the fixed effects model. The SMD is the difference between the two means divided by the pooled standard deviation, with a correction for small sample bias. Next the heterogeneity statistic is incorporated to calculate the summary SMD under the random effects model. The total SMD with 95% CI is given both for the Fixed effects model and the Random effects model.

The SMD has no units or dimensions, however using Cohen's rule of thumb for interpretation of the SMD statistic: a value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect, and a value of 0.8 or larger indicates a large effect.

3. Results

3.1. Systematic Review

From all databases 465 relevant articles were identified with 390 articles remaining after removal of duplicates. After applying inclusion criteria, 375 were removed and 15 articles remained. These included 15 RCTs [30,36–49], nine new RCTs and six identified by previous reviews. Seven of the 15 were published in 2011 and 2012 (Table 1).

There was wide variation in study methodology. The study populations were diverse (Table 1). Smaller studies were performed in patients with specific disorders (depression, seasonal affective disorder, obesity, post-menstrual tension and hospitalized patients) [30,37–39,41–44,47–49], and studies in University students [45,46].

Table 1. Study populations, sample sizes (numbers entering intervention and control groups respectively) and methodological quality score (PEDro Scale).

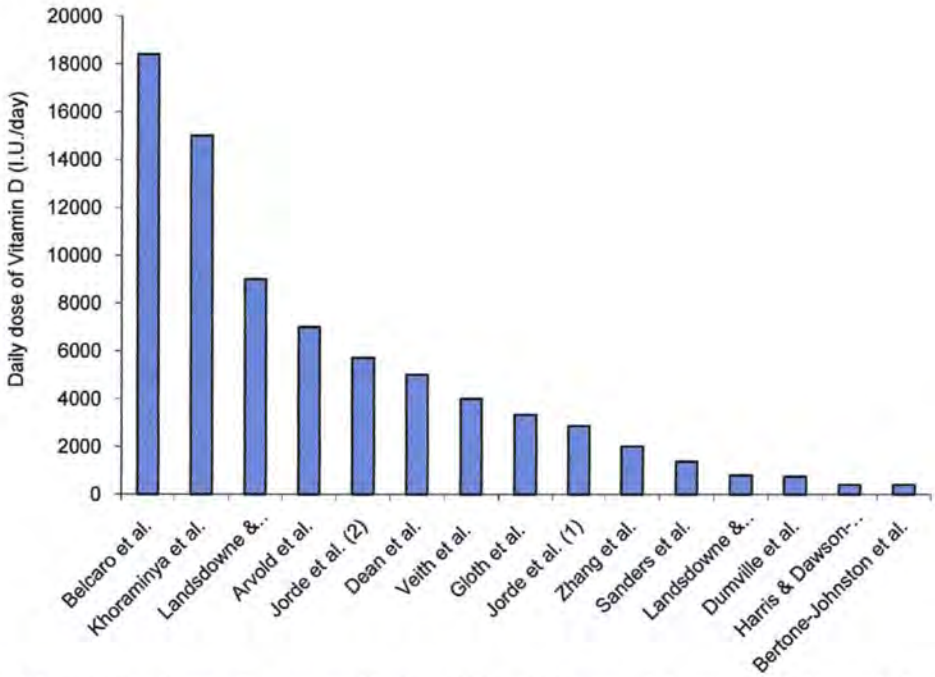
Author	Year	Reference Citation #	Population	Sample Size	Quality Score
Arvold *et al.*	2009	[36]	Individuals with Vit D deficiency (10–25 ng/mL) seen for medical care at a primary healthcare clinic	100 (I 50, C 50)	10
Belcaro *et al.*	2010	[42]	Menopausal women with signs of depression and mood disorder	65 (I 33, C 32)	8
Bertone-Johnson *et al.*	2012	[38]	Postmenopausal Women with depressive symptoms	36,282 (I 18176, C 18106)	11
Dean *et al.*	2011	[45]	Young healthy adults (University students)	128 (I 63, C 65)	11
Dumville *et al.*	2006	[43]	Older women with seasonal affective disorder	2117 (I 912,C 1205)	11
Gloth *et al.*	1999	[44]	Adults with Season Affective Disorder	15 (I 8,C 7)	6.5
Harris & Dawson-Hughes	1993	[30]	Women with seasonal affective disorder	250 (I 125, C 125)	5
Jorde *et al.*	2008	[37]	Overweight and obese adults	441 (IH 150, ILl 142, C 149)	8
Khajehei *et al.*	2009	[46]	University female students with premenstrual syndrome	180 (IOes 60, I 60, C 60)	9
Khoraminya *et al.*	2013	[49]	Adults with major depressive disorder based on DSM-IV criteria, without psychosis	40 (I 20, C 20)	10
Landsdowne & Provost	1998	[39]	Adults with seasonal affective disorder	44 (I 22, C 22)	8
Sanders *et al.*	2011	[47]	Community dwelling older women with seasonal mood disorders	2012 (I 1001, C 1011)	11
Veith *et al.*	2004	[40]	Adults with serum 25(OH)D <61 nmol/L in summer, expected to develop 25(OH)D concentrations <40 nmol/L by winter	64 (I 32, C 32)	10
Yalamanchilli & Gallagher	2012	[48]	Older post-menopausal women with depression	488 (Ioes+Calcitrol 122, Ioes 122, Calcitrol 123, placebo 123)	11
Zhang *et al.*	2011	[41]	Hospitalized patients	32 (I 17, C 15)	9

C = control group and I = intervention group. Where there are two intervention groups; IH is used to indicate where a high dose and IL for where a low dose of Vitamin D supplements were given. Where one intervention group took a hormone, this was designated IOes.

Baseline 25OHD levels were not reported in six papers [36–41] but were performed in eight studies [42–49] (Table 2). For one study [30], Vitamin D data was sought from an earlier paper [50] showing 25OHD levels were not measured at baseline. However 25OHD levels were measured twice during the study. This demonstrated that the 25OHD levels decreased 5% in the intervention group during this part of the study due to the decreased availability of sunlight with the change in season, overwhelming the effect of the low dose of Vitamin D supplements provided.

Daily doses varied from 400 I.U. to 18,400 I.U. across the 15 trials (Figure 1). Three studies [30,38,43] used doses lower that 800 I.U./day. In the Women's Health Initiative [38], the Vitamin D dose would be inadequate to change vitamin levels; the actual dose ingested was ≈200 I.U., as the stipulated dose was 400 I.U. but compliance was 46%. The doses shown in two papers were misprints; reported as 200 mg Vitamin D [42] and 0.25 g of calcitriol [48], equating to millions of international units. However, attempts to clarify this with authors and editors were unsuccessful. The intervention in another study [47] was high dose Vitamin D (500,000 I.U.) probably inducing side effects; a 15% increase in falls and 26% increase in fractures.

Figure 1. Daily dose of Vitamin D per study. This shows the range of equivalent daily doses. (These were calculated after estimating the actual dose rather than using the dose shown in their published papers).



Low doses of 400 I.U. in Harris & Dawson-Hughes [30] and Bertone-Johnson *et al.* [38]; High doses were over 15,000 I.U. per day in Belcaro *et al.* [42] and Khoraminya *et al.* [49]; Jorde *et al.* [37] and Landsdowne & Provost [39] both tested three groups; two differing dosages and one placebo.

Validated outcome measures of depression (Table 2) included Beck Depression Index in three studies [37,45,49] the Profile of Mood States in two studies [30,41] and the mental component score of the SF12 in two studies [43,47]. Questionnaires about pre-menstrual syndrome [46], fibromyalgia [36], and menopause [42] included depression as a domain. One early study used an unvalidated questionnaire [39]. There was no significant differences at baseline measures and methodological quality of studies was generally high (9 out of 11) (Table 1).

Table 2. Key depression outcome measures, within and between group findings.

Author	Year	Outcome Measures	Follow-up Time Period	Within Group Findings	Between Group Findings
Arvold *et al.*	2009	Fibromyalgia Impact Questionnaire	8 weeks	FIQ score Mean pre-post difference total (95%CI) intervention −3.71 (−7.5 to 0.1) ($p < 0.03$), control 1.91 (−2.9 to 6.7) ($p > 0.05$)	$p < 0.05$ favoring intervention
Belcaro *et al.*	2010	Menopause Symptoms Questionnaire	8 weeks	Total average symptom score reduced by 48% for intervention group ($p < 0.05$), control group increased by 10% ($p > 0.05$).	$p < 0.05$ favoring intervention
Bertone-Johnson *et al.*	2012	Burnam Depression Scale	At 2 weeks, then twice yearly for 2 years	Mean overall change (SD) 0.004 (0.143) intervention, −0.002 (0.113) (control)	$p > 0.05$
Dean *et al.*	2011	Beck Depression Index	6 weeks	Baseline: follow up mean (95%CI): Intervention 7.24 (5.58–8.90); 6.40 (4.73–8.07) ($p > 0.05$); control 5.72 (4.09–7.36); 5.38 (3.74–7.02) ($p > 0.05$)	$p > 0.05$
Dumville *et al.*	2006	SF12 mental component	6 months	Mean difference (95%CI) between intervention and control at baseline −0.6 (−1.5 to 0.3) ($p > 0.05$); at follow up 1.8 (−0.8 to 1.2) ($p > 0.05$)	Mean adjusted (age- and baseline score) between group difference (95%CI) −0.49 (−1.34 to 0.81) $p > 0.05$
Gloth *et al.*	1999	SAD-8	1 month	Significant improvement in SAD-8 scores for intervention group, not control (explanatory data not provided)	Significant association between improvement in Vit D levels and SAD-8 scores in overall cohort ($r^2 = 0.26$)
Harris & Dawson-Hughes	1993	Profile of Mood States	3 monthly for 12 months	No difference in pre-post scores for any domain of PoMS for either intervention or control ($p > 0.05$)	No difference between intervention or control change over time in any domain ($p > 0.05$)
Jorde *et al.*	2008	Beck Depression Index (total score)	12 months	Baseline: DD group 4.5 (0.0-24.0); DP group 5.0 (0.0–28.0); PP group 4.0 (0.0–24.0). Follow-up: DD group 3.0 (0.0–23.0) ($p < 0.05$); DP group 4.0 (0.0–26.0) ($p < 0.05$); PP group 3.8 (0.0–18.0)	DD and DP groups change was similar ($p > 0.05$) but significantly greater from PP ($p < 0.05$)

Table 2. *Cont.*

Author	Year	Outcome Measures	Follow-up Time Period	Within Group Findings	Between Group Findings
Khajehei *et al.*	2009	PMS symptom rating form which captured psychological and physical symptoms including depression	Pre-mens for 2 cycles	Mean % total symptoms *Pre:* Dydrogesteron group 52.1%, Calcium plus Vitamin D group 50.7%, Placebo 53.7%. *Post* (respectively): 47.9%, 46.1%, 53.7% Both active treatment groups had significant decreases	The dydrogesterone and calcium plus Vitamin D treatments were significantly more effective than placebo in lessening the severity of PMS symptoms ($p < 0.05$)
Khora-minya *et al.*	2013	24-item Hamilton Depression Rating Scale (HDRS) (1°), 21-item Beck Depression Inventory (BDI) (2°)	Every 2 weeks for 8 weeks	BDI Intervention Wk0 32.45 ± 7.35; Wk2 27.73 ± 7.50; Wk4 20.44 ± 6.56; Wk6 16.73 ± 8.11; Wk8 13.2 ± 8.64 ($p < 0.05$) Control. Wk0 31.65 ± 7.33; Wk2 29.17 ± 6.78; Wk4 25.18 ± 6.93; Wk6 21.00 ± 6.81; Wk8 17.95 ± 6.31 ($p < 0.05$)	$p < 0.05$ for both outcomes, favoring intervention
Lands-downe & Provost	1998	PANAS	5 days	Sig within-group improvements for both active interventions ($p < 0.05$)	Sig improvements for both active interventions cf control for positive and negative affects ($p < 0.05$)
Sanders *et al.*	2011	General Health Questionnaire SF12 (PCS, MCS), WHO Wellbeing Index	3–5 years	Intervention: no intervention SF12 PCS effect size (95%CI) 0.27 (−2.40 to 2.94) 0.23 (−0.88 to 1.34)	Treatment effects SF12 effect size (95%CI) PCS 0.22 (−70.75 to 1.19); MCS 70.14 (−71.00 to 0.72)
Veith *et al.*	2004	Self-developed Wellbeing Scale	2–6 months	Pre-post mean (SD): *600 I.U.* 2.2 (2.0); 2.3 (2.3) ($p > 0.05$) *4000 I.U.* 2.0 (2.3); 1.1 (1.8) ($p < 0.05$)	Significant improvement in wellbeing, favoring higher Vit D dose

Table 2. *Cont.*

Author	Year	Outcome Measures	Follow-up Time Period	Within Group Findings	Between Group Findings
Yalamanchilli & Gallagher	2012	Geriatric Depression Scale	1. HT alone 2. calcitriol alone 3. HT & calcitrol 4. placebo	*% with depression* (pre/post) 13.8%; 8.9%; 9.7%; 7.3%; 8.2%; 6.6% 13.8%; 8.9% All groups $p > 0.05$	No effect on depression in any treatment group compared with placebo ($p > 0.05$)
Zhang *et al.*	2011	Profile of Mood States questionnaire	Average 8 days	Vit D group pre-post 23.1 ± 27.2; 22.4 ± 22.4 $p > 0.05$ Vit C group pre-post 28.6 ± 21.8; 18.8 ± 19.4) $p < 0.05$	$p < 0.05$ favouring Vit D

3.2. Biological Flaws

Biological flaws were found in eight of the 15 studies (Table 3). These flaws limit the ability of these studies to demonstrate a change in vitamin status in the intervention group. The most common flaw, occurring in five studies, was not measuring 25OHD. Two studies [30,38] utilized doses below the minimum effective dose of 600-800 I.U. [51] and one study [45] had such high baseline 25OHD levels that supplements could not improve the Vitamin D status of participants. One intervention was associated with a decrease in 25OHD level [30], and another caused falls and fractures minimising the potential to see any health benefits [47]. Biological flaws were more prevalent (70%) in recent studies (since 2010) than in earlier studies (50%), and in larger studies than in smaller studies (Table 3).

Table 3. Comparison of studies by presence of biological flaws to the study findings and methodological quality.

Study	Biological Flaws NOT Present	Biological Flaw(s) Present	Type of Flaw		Quality Score (Max 11)	Date of Publication	
			25OHD not Assessed	*Dose not Appropriate*			
Belcaro *et al.*		X	X		8		2010
Bertone-Johnson *et al.*		X	X	X (L)	11		2012
Dumville *et al.*		X	X		11	2006	
Harris & Dawson-Hughes		X	X	X (L)	5	1993	
Dean *et al.*		X	X	X (H)	11		2011
Khajehei *et al.*		X		X (I)	9	2009	
Sanders *et al.*		X		X (SE)	11		2011
Yalamanchilli & Gallagher		X		X (I)	11		2012
Total-8 Studies with Biological Flaws	**0**	**8**	**5**	**6**		**3**	**5**
Arvold *et al.*	**X**				***10***	2009	
Gloth *et al.*	**X**				6.5	1999	
Jorde *et al.*	**X**				8	2008	
Khoraminya *et al.*	**X**				10		2013
Landsdowne & Provost	**X**				8	1998	
Veith *et al.*	**X**				10	2004	
Zhang *et al.*	**X**				9		2011
Total—7 studies without flaws	7	**0**	**0**	**0**		**5**	**2**

↑ = significant improvement favouring Vitamin D; Dose incorrect (I), low (L), high (H) or produces side effects (SE).

Of the seven studies without flaws, six [36,37,39,40,44,49] showed improvement in depression with supplementation, whereas six of the nine flawed studies [30,38,42,45–48] had a null result (Table 3). The positive results in two flawed studies maybe due to the unknown contents [46] or the effects of the herbs [42] used in these studies.

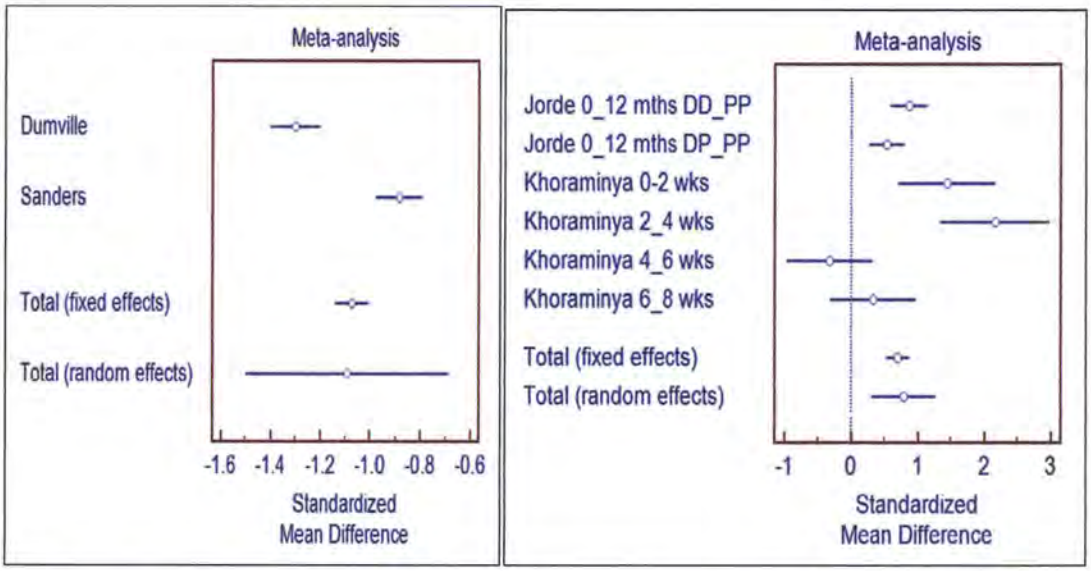
3.3. Meta-Analysis

3.3.1. Meta-Analysis of Studies without Biological Flaws (Right Panel of Figure 2)

Two studies (Jorde *et al.* [37] and Khoraminya *et al.* [49]) were included as they used the same outcome measure; the Beck Depression Inventory.

The standardized mean difference for these studies without flaws is shown in the Right Panel of Figure 2. It shows a statistically significant positive effect of Vitamin D in depression of 0.78 (CI 0.24, 1.27). The random effects model was used due to the diverse populations studied.

Figure 2. The figures show the meta-analysis of studies from the systematic review.



Left Panel—Two studies with biological flaws were combined, Dumville *et al.* [43] and Sanders *et al.* [47]; **Right Panel**—Two studies without biological flaws were combined, Jorde *et al.* [37] and Khoraminya *et al.* [49], showing two intervention groups for Jorde *et al.* [37] (high and low dose Vitamin D) and the data from the Khoraminya *et al.* [49] at 2, 4, 6, and 8 weeks.

The Jorde *et al.* [37] trial ($n = 387$) had three study groups; two interventions with different doses of Vitamin D and a control. The Khoraminya *et al.* [49] trial ($n = 40$) compared Vitamin D plus fluoxetine to fluoxetine alone. The studies had similar baseline level of 25OHD (Jorde *et al.* [37] 55 nmol/L) (Khoraminya *et al.* [49] 57 nmol/L), and the doses of Vitamin D over 800 nmol/L in both studies. The participants in both studies were patients; Khoraminya *et al.* [49] depressed patients and Jorde *et al.* [37] obese patients. Depression and obesity overlap, as there is a reciprocal relationship between obesity and depression indicated by the 50% increase in one condition when the other is present [52].

3.3.2. Meta-Analysis of Studies with Biological Flaws (Left Panel of Figure 2)

Options for meta-analysis were examined and performed combining the Dumville *et al.* [43] and Sanders *et al.* [47] studies, due to the diverse outcome variables used in other studies. There was a statistically significant negative effect of Vitamin D administration evident from the forest plot in the

standardized mean differences as shown in the Left Panel of Figure 2. The effect size was −1.1 (CI −0.7, −1.5) (random effects). These studies were of high methodological quality, had similar subjects (community dwelling women aged >70 years) and baseline 25OHD, and used the same outcome measure. The studies differed in the dosing schedule, daily and annually.

4. Discussion

This is the most comprehensive systematic review of randomized controlled trials investigating the effectiveness of Vitamin D in the management of depression. Fifteen RCTs were found, whilst previous reviews captured few of the available RCTs. Although the methodological quality was good, biological flaws were common and more prevalent in recent studies.

For the meta-analysis of studies without biological flaws, the size of the effect was statistically significant being +0.78 (CI 0.24, 1.27). As the measure of effect size was the standardized mean difference (SMD), this was 0.78, using Cohen's Rule-of-Thumb, a SMD of 0.8 is considered to indicate a large effect.

As less than half the study population were deficient the effect of the intervention was diluted such that if all subjects had been deficient the size of the effect would have been higher, perhaps double, 1.5 points on the BDI scale. This is similar to the size of effect seen in a large RCT of antidepressant medication, which was 0.8 point on the BDI scale for the blinded parts of the study and 1.7 points overall [53]. A review of antidepressant efficacy published in the NEJM [54] shows that the effect size of antidepressant medication was increased by selective publication of trials and altering the effect size. However the overall mean weighted effect size value for antidepressants was only 0.15 (CI 0.08, 0.22) for unpublished studies and 0.37 (CI 0.33, 0.41) for published studies. Thus, the effect size of Vitamin D demonstrated in our meta-analysis may be comparable with that of anti-depressant medication. For the meta-analysis of studies with biological flaws, the size of the effect was statistically significant and negative being −1.1 (CI −0.7, −1.5), indicating that Vitamin D supplementation in flawed studies may lead to deterioration in depression.

The main finding is that all studies without flaws and the meta-analysis of studies without biological flaws support the efficacy of Vitamin D supplementation for depression, as compared with the negative results of meta-analysis for studies with biological flaws. The Womens Health Initiative [38] (WHI), with more participants that all the other studies combined, had the highest methodological quality and the most biological flaws leading to non-significant outcomes for both bone strength and mood. Due to its sheer size, the WHI has dominated previous meta-analysis leading to null results.

The main limitation of this review was the diversity of study methodology precluding more extensive meta-analyses, and leaving only two studies in each meta-analysis. The variability in outcome measures and reporting suggest agreement should be sought within the research community to underpin standard conduct and reporting of future studies to support meta-analysis.

5. Conclusion

Traditional evidence, biological plausibility and epidemiological studies indicate Vitamin D has therapeutic effects in depression. There are no previous meta-analyses of Vitamin D and depression as

the evidence was deemed to be insubstantial [25]. This may be due to previous systematic reviews identifying few of the available studies and including RCTs with inappropriate methodology and biological flaws.

Meta-analysis of studies without biological flaws demonstrates that improving Vitamin D levels improves depression, whereas the meta-analysis of flawed studies had a negative result. Heaney [34] identified the most common flaw "baseline status" and the most pernicious flaw "(in)effective dosing". However we found other flaws: not measuring 25OHD levels throughout the study limits the ability to know if the 25OHD level actually changed. In this case, there would be no reason to believe that the intervention caused a biological difference in Vitamin D levels between intervention and control groups. We also found more fundamental biological flaws where the intervention was not Vitamin D but calcium, and caused a decreased in the 25OHD level. These two studies were included in previous systematic reviews but rejected by this review.

The finding that meta-analyses for studies with biological flaws had the statistically significant effect of increasing depression, may lead to a conclusion that some of these trials led to levels for Vitamin D above the therapeutic range. This would be supported by a recent paper indicating that the therapeutic range for 25OHD in depression is 50 and 85 nmol/L [55].

It may be argued that meta-analysis including flawed RCTs reflect the trial methodology more than the efficacy of the intervention, leaving reviewers unable to make valid conclusions about efficacy [34], resulting in uncertainty amongst researchers and clinicians. This has led to calls for more RCTs and less "torturing of the data" by meta-analysis [56]. However, as this review demonstrates, it is excluding biological flaws that will lead to greater understanding of Vitamin D, not simply increasing the quantity of studies.

We note that biological flaws are more frequent in recent studies; this may be due to the belief that vitamins exert a function beyond deficiency. Hence RCTs should test whether using supplementation to correct deficiency is beneficial, rather than testing whether additional supplementation on top of the recommended doses is beneficial in reducing disease [57]. Thus, it is unremarkable that Vitamin D supplementation would not benefit a population that are not deficient or where the dose was ineffective. To test the hypothesis that correcting Vitamin D deficiency leads to an improvement in depression, it is critical to exclude biological flaws from future studies.

The effect size for Vitamin D in depression demonstrated in this meta-analysis is comparable with the effect of anti-depressant medication, an accepted treatment for depression. Should these results be verified by future research, these findings may have important clinical and public health implications.

Acknowledgments

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House Bill 39

Sectional

Section 1

This section includes legislative findings and intent language which states that we can prevent disease by lowering the incidence of disease, and that preventing disease will slow the rate of health care cost to the State.

Section 2

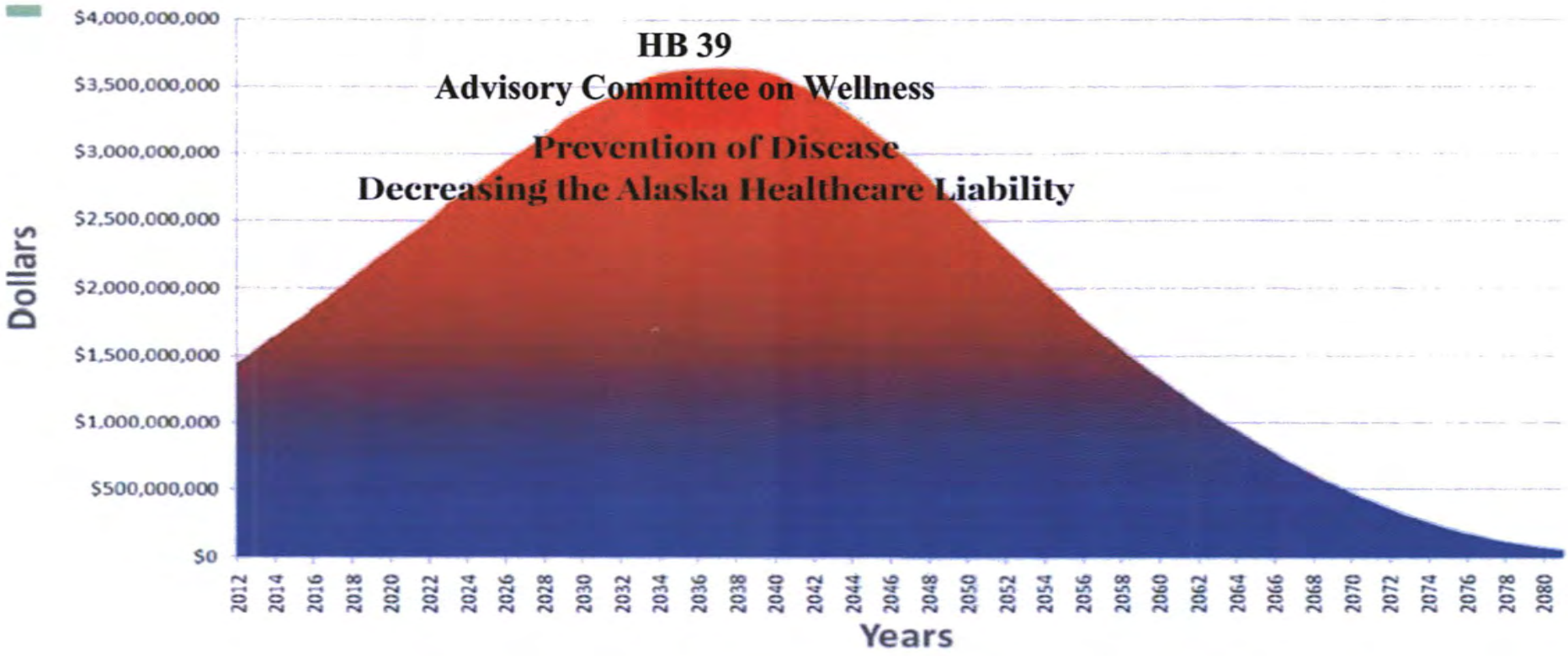
This section requires the Department of Administration, to the extent legally and reasonably practicable, to implement the recommendations of the Advisory Committee on Wellness and reduce the escalation of health care costs. This section of statute applies to state life and health insurance plans.

Section 3

This section requires the Department of Administration, to the extent legally and reasonably practicable, to implement the recommendations of the Advisory Committee on Wellness and reduce the escalation of health care costs. This section of statute applies to self-insurance and excess loss insurance.

Section 4

This section establishes the Advisory Committee on Wellness in the Department of Administration, outlines the appointment and roles of committee members, and requires the commissioner of administration to respond to the committee within six months.


HB 39
Advisory Committee on Wellness
Prevention of Disease
Decreasing the Alaska Healthcare Liability
Dollars
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Years

$3.8 BILLION

$3.8 Billion is the amount of our PERS/TRS unfunded liability attributable to healthcare according to the Department of Administration.

The old estimate for a 2% annual, out-year, healthcare cost increase was used for setting the contribution rates to fully cover anticipated liabilities.

So this $3.8 billion represents the healthcare cost inflation above 2%.

STATE OF ALASKA

Why are we here?

The State of Alaska is a significant health care consumer.

Active plan	**17,144 members** (includes dependents)	**$111 million** total spend in FY13
Retiree plan	**64,237 members** (includes dependents) 40% live outside Alaska	**$492 million** total spend in FY13
Medicaid	**145,279 Alaskans covered (2013)** 58% children, 36% adults, 6% seniors	**$1.6 billion** total spend in 2013

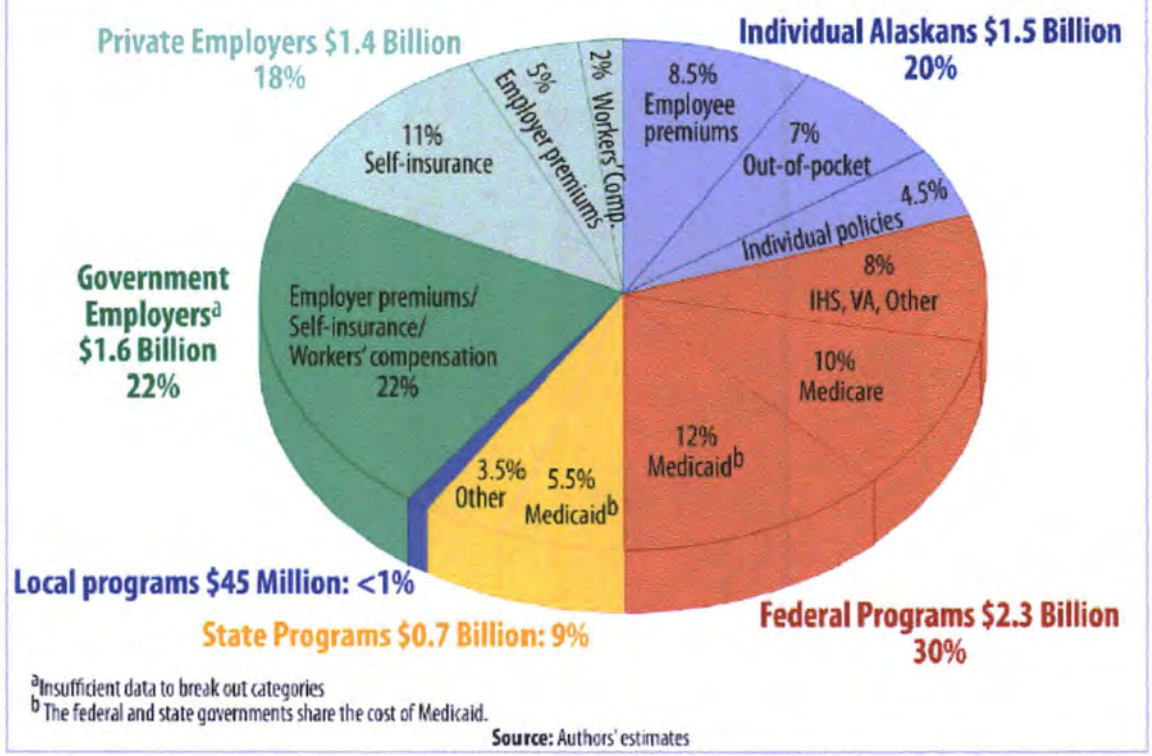
The state also spends money on health care for inmates, state employees who are members of union health trusts and for state workers' compensation claims.

Alaska's Health-Care Bill: $7.5 Billion and Climbing

By Mark A. Foster and Scott Goldsmith

UA Research Summary No. 18 • August 2011
Institute of Social and Economic Research • University of Alaska Anchorage

Figure 1. Who Pays for Health Care in Alaska?
(2010 Spending: $7.5 Billion)



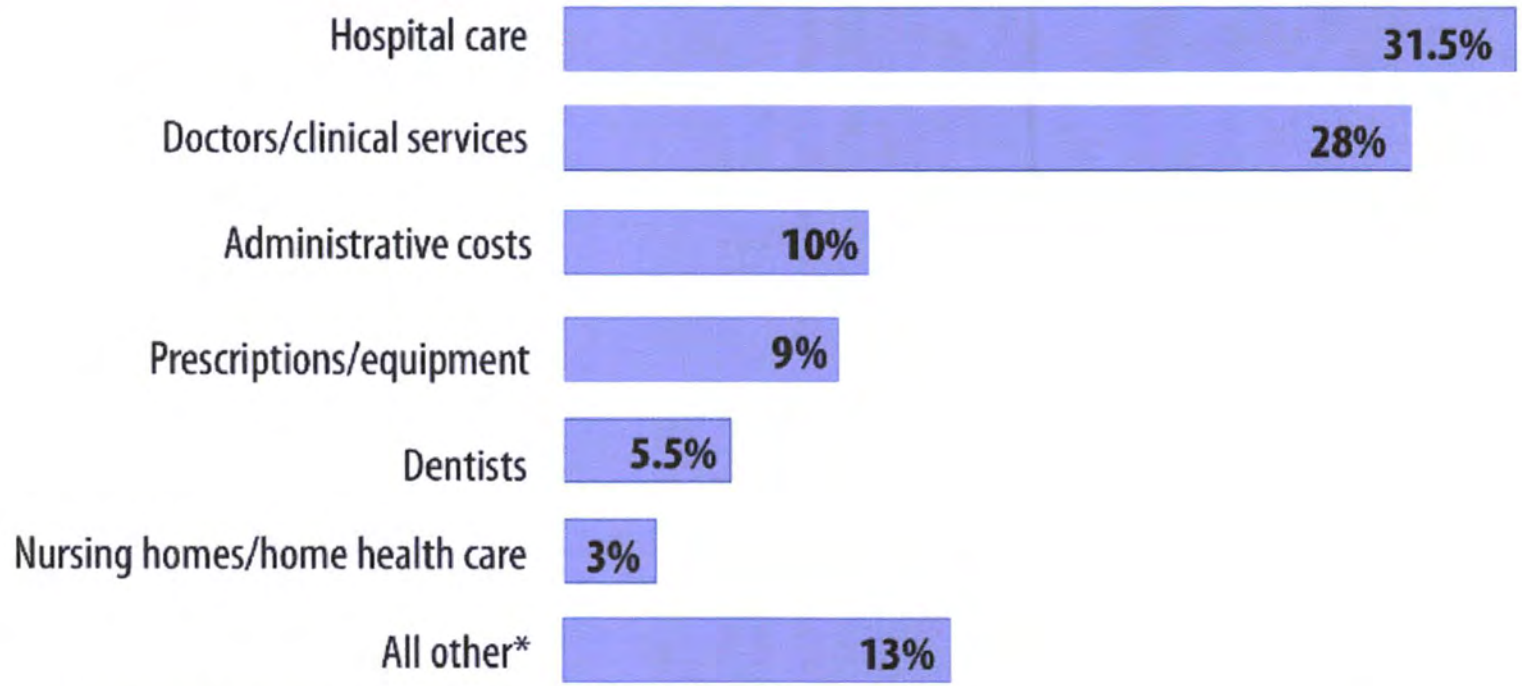
[a] Insufficient data to break out categories
[b] The federal and state governments share the cost of Medicaid.

Source: Authors' estimates

Health-care spending for Alaskans reached about $7.5 billion in 2010. For comparison, that's close to half the wellhead value of all the oil produced in Alaska that year. It's also roughly equal to half the wages Alaskans collected in 2010.

Figure 7. What Do Alaska's Health-Care Dollars Buy?

(2010 Spending: $7.5 Billion)



*Other personal and professional care and public health activities.

Source: Mark A. Foster and Associates estimates, based on Centers for Medicare and Medicaid Services, National Health Expenditure accounts

The Question:

How CAN WE AVOID diseases and PREVENT illness instead of just reacting to and paying for SICKCARE?

The following slides demonstrate that we can reduce healthcare costs by initiating policies to avoid diseases with scientifically documented strategies, including vitamin D. The following is only an example of one the many wellness policies the committee might recommend.

HealthSmart
CARE MANAGEMENT SOLUTIONS

ACTIVE PLAN

4th Quarter Report 2013

Aggregate Risk Profile

Member Information			
Member Count	17338	Avg Forecasted Cost	$6,670
Avg Age	35	Avg Total Cost	$6,774
Percent Female	51%	Avg Forecasted Risk Index	1.09
Avg Months Enrolled	11	%/w Acute Impact Score >= 95	1.06%
		%/w Chronic Impact Score >= 95	5.38%
		%/w Motivation Rank >= 95	4.83%

Aggregate Risk Summary					
Risk Drivers	# Members	Avg Risk Contribution		Contribution to Forecast	Risk Contribution
Demographics	17338	SENIORS SKIN, FRACTURES, FALLS	$345	$5,987,784	5.18% X
Acute Respiratory Disorders	2880	TUBERCULOSIS	$1,129	$3,251,578	2.81% X
Arrhythmia Disorders	220		$3,382	$744,142	0.64%
CHF Conditions	673	CHRONIC HEART FAILURE	$3,181	$2,140,732	1.85% X
Cerebral Vascular Disorder	247		$4,199	$1,037,177	0.90%
Chronic Respiratory Disorders	1728	UPPER RESPIRATORY TRACT	$2,318	$4,005,542	3.46% X
Coronary Artery Related Conditions	1655	CORONARY HEART DISEASE	$2,958	$4,895,538	4.23% X
Dermatological Disorder	3075		$1,272	$3,911,805	3.38%
Diabetic Disorders	882	TYPE 1 AND TYPE 2	$5,932	$5,231,998	4.52% X
Female Reproductive Conditions	341	PRETERM BIRTHS	$2,510	$856,045	0.74% X
Gastrointestinal Disorders	2351	COLORECTAL CANCER	$2,011	$4,728,854	4.09% X
Heart Related Conditions	180		$5,628	$1,013,046	0.88%
Hypertension	1527	BLOOD PRESSURE	$1,983	$3,028,315	2.62% X
Hypotensive Drugs	1784		$2,207	$3,937,924	3.41%
Major Infection Related Conditions	2950	MRSA	$2,023	$5,968,497	5.16% X
Metabolic Conditions	3077	FIBROMYALGIA	$2,680	$8,247,421	7.13% X
Minor Infection Related Conditions	3704		$1,340	$4,965,037	4.29%
Miscellaneous Conditions	4750		$2,303	$10,940,696	9.46%
Musculo-skeletal Disorders	5173	INFANT MUSCLE, SENIOR FALLS	$2,206	$11,409,047	9.87% X
Myocardial Infarction Related Conditions	271		$5,315	$1,440,328	1.25%
Neonatal Issues	255	AUTISM, HEART PROGRAMMING	$935	$238,299	0.21% X
Neoplastic Related Conditions	638		$4,332	$2,763,900	2.39%
Neurological Disorder	3770	ALZHEIMER'S	$1,435	$5,409,047	4.68% X
Non-specific condition	5561		$140	$780,877	0.68%
Pneumonia	243	UPPER RESPIRATORY TRACT	$3,822	$928,744	0.80% X
Psychological Disorder	2688	S.A.D. AND DEPRESSION	$2,771	$7,447,883	6.44% X
Renal Disorders	309		$15,145	$4,679,794	4.05%
Trauma Related Condition	1822	TRAUMATIC BRAIN INJURY	$1,455	$2,651,019	2.29% X
Urinary Disorders	1381		$2,170	$2,996,360	2.59%

% total diseases directly related to Vitamin D status = 66.08 %

Notes in red by office of Rep. Seaton

RETIREE PLAN

HealthSmart CARE MANAGEMENT SOLUTIONS

4th Quarter Report 2013

Aggregate Risk Profile

Member Information			
Member Count	65376	Avg Forecasted Cost	$15,666
Avg Age	63	Avg Total Cost	$17,726
Percent Female	54%	Avg Forecasted Risk Index	2.56
Avg Months Enrolled	12	%/w Acute Impact Score >= 95	5.47%
		%/w Chronic Impact Score >= 95	16.63%
		%/w Motivation Rank >= 95	9.70%

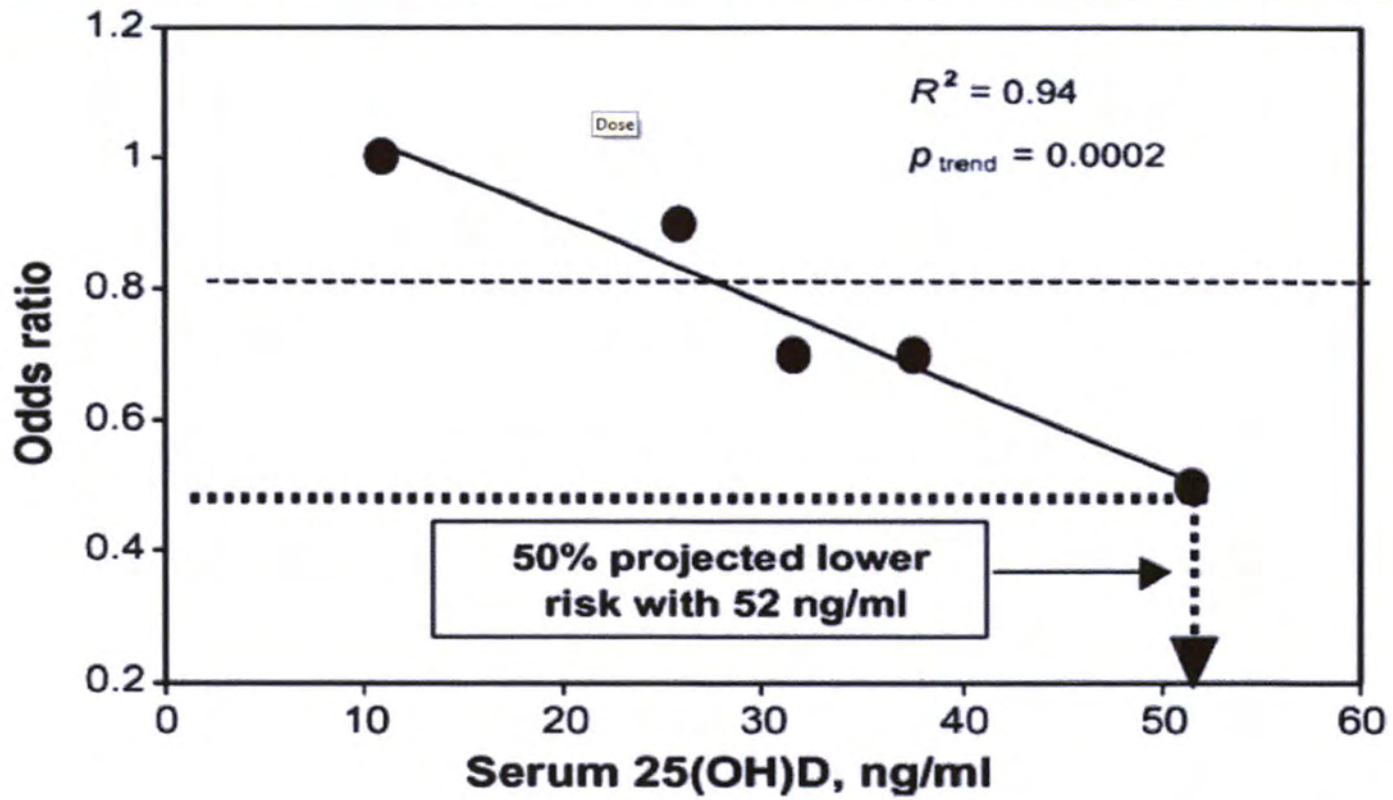
Aggregate Risk Summary					
Risk Drivers	# Members	Avg Risk Contribution		Contribution to Forecast	Risk Contribution
Demographics	65376	SENIORS SKIN, FRACTURES, FALLS	$454	$29,702,943	2.90% X
Acute Respiratory Disorders	9520	TUBERCULOSIS	$1,669	$15,893,121	1.55% X
Arrhythmia Disorders	5170		$2,860	$14,786,038	1.44%
CHF Conditions	10658	CHRONIC HEART FAILURE	$2,758	$29,389,999	2.87% X
Cerebral Vascular Disorder	5021		$3,726	$18,710,595	1.83%
Chronic Respiratory Disorders	11241	UPPER RESPIRATORY TRACT	$3,093	$34,763,411	3.39% X
Coronary Artery Related Conditions	24057	CORONARY HEART DISEASE	$2,900	$69,776,210	6.81% X
Dermatological Disorder	15979		$1,958	$31,281,265	3.05%
Diabetic Disorders	10689	TYPE 1 AND TYPE 2	$5,966	$63,771,119	6.23% X
Female Reproductive Conditions	103	PRETERM BIRTHS	$1,489	$153,413	0.01% X
Gastrointestinal Disorders	18753	COLORECTAL CANCER	$2,146	$40,246,314	3.93% X
Heart Related Conditions	4346		$4,374	$19,007,254	1.86%
Hypertension	21394	BLOOD PRESSURE	$1,623	$34,713,887	3.39% X
Hypotensive Drugs	21282		$1,869	$39,772,355	3.88%
Major Infection Related Conditions	13879	MRSA	$3,007	$41,731,745	4.07% X
Metabolic Conditions	28763	FIBROMYALGIA	$2,545	$73,213,862	7.15% X
Minor Infection Related Conditions	14339		$1,726	$24,754,410	2.42%
Miscellaneous Conditions	32888		$2,762	$90,833,634	8.87%
Musculo-skeletal Disorders	32886	INFANT MUSCLE, SENIOR FALLS	$2,498	$82,154,255	8.02% X
Myocardial Infarction Related Conditions	5796		$3,424	$19,844,208	1.94%
Neonatal Issues	63	AUTISM, HEART PROGRAMMING	$1,504	$94,751	0.01% X
Neoplastic Related Conditions	7447		$3,928	$29,253,071	2.86%
Neurological Disorder	27775	ALZHEIMER'S	$1,561	$43,366,164	4.23% X
Non-specific condition	12687		$113	$1,429,752	0.14%
Pneumonia	1619	UPPER RESPIRATORY TRACT	$5,098	$8,254,358	0.81% X
Psychological Disorder	16031	S.A.D. AND DEPRESSION	$2,659	$42,623,390	4.16% X
Renal Disorders	4750		$16,668	$79,174,484	7.73%
Trauma Related Condition	8749	TRAUMATIC BRAIN INJURY	$1,904	$16,660,268	1.63% X
Urinary Disorders	11515		$2,504	$28,836,425	2.82%

% total diseases directly related to Vitamin D status = 61.16%

Notes in red by office of Rep. Seaton

Meta-analysis of breast cancer risk

[Slide by Cedric F. Garland, et al. University of California San Diego]



Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.

Active State Of Alaska employees, Retirees and dependents - **83,000**

Female percentage of AK employees and retirees: 53% = 43,990

Incidence of Breast Cancer per year in AK - **125 per 100,000 (.0125)**

Average cost of annual medical expenditures directly attributable to Breast Cancer - **$11,000**

=

Per year AK State Cost for Breast Cancer: **$6,048,625**

50% reduction with vitamin D
Per Year Savings with vitamin D:

$3,024,312

72% reduction with vitamin D (2014 GRH study)
Per Year Savings with Vitamin D:

$4,355,010

Meta-analysis

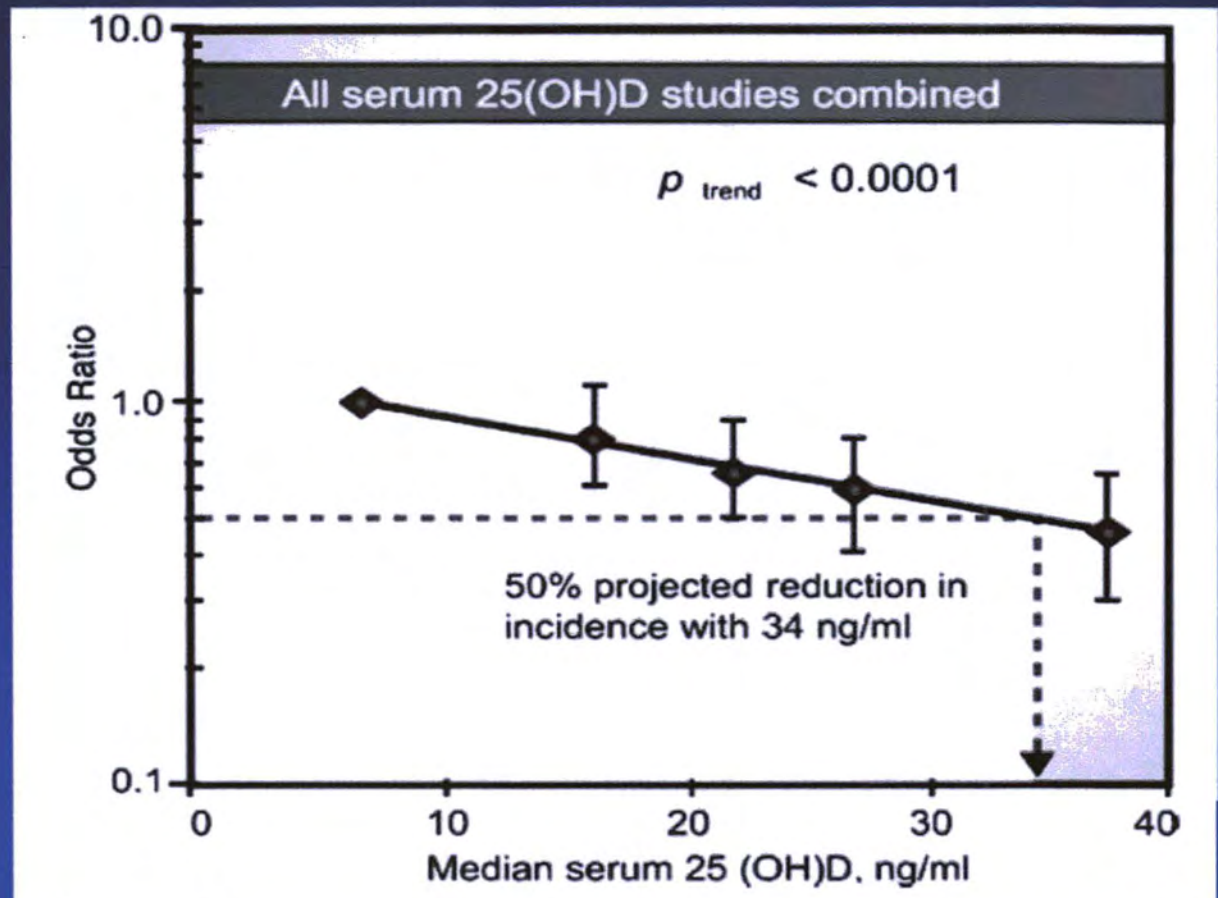


Figure 1. Dose–response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined.[1,4–7] The five points are the odds ratios for each quintile of 25(OH)D based on combined data from the five studies.

Optimal Vitamin D Status for Colorectal Cancer Prevention Edward D. Gorham, et al. Am J Prev Med; 2007

Active State Of Alaska employees, Retirees and dependents - **83,000**

Incidence of Colorectal Cancer per year in AK - **43 per 100,000 (.0043)**

Average cost of annual medical expenditures directly attributable to Colon Cancer - **$ 11,000**

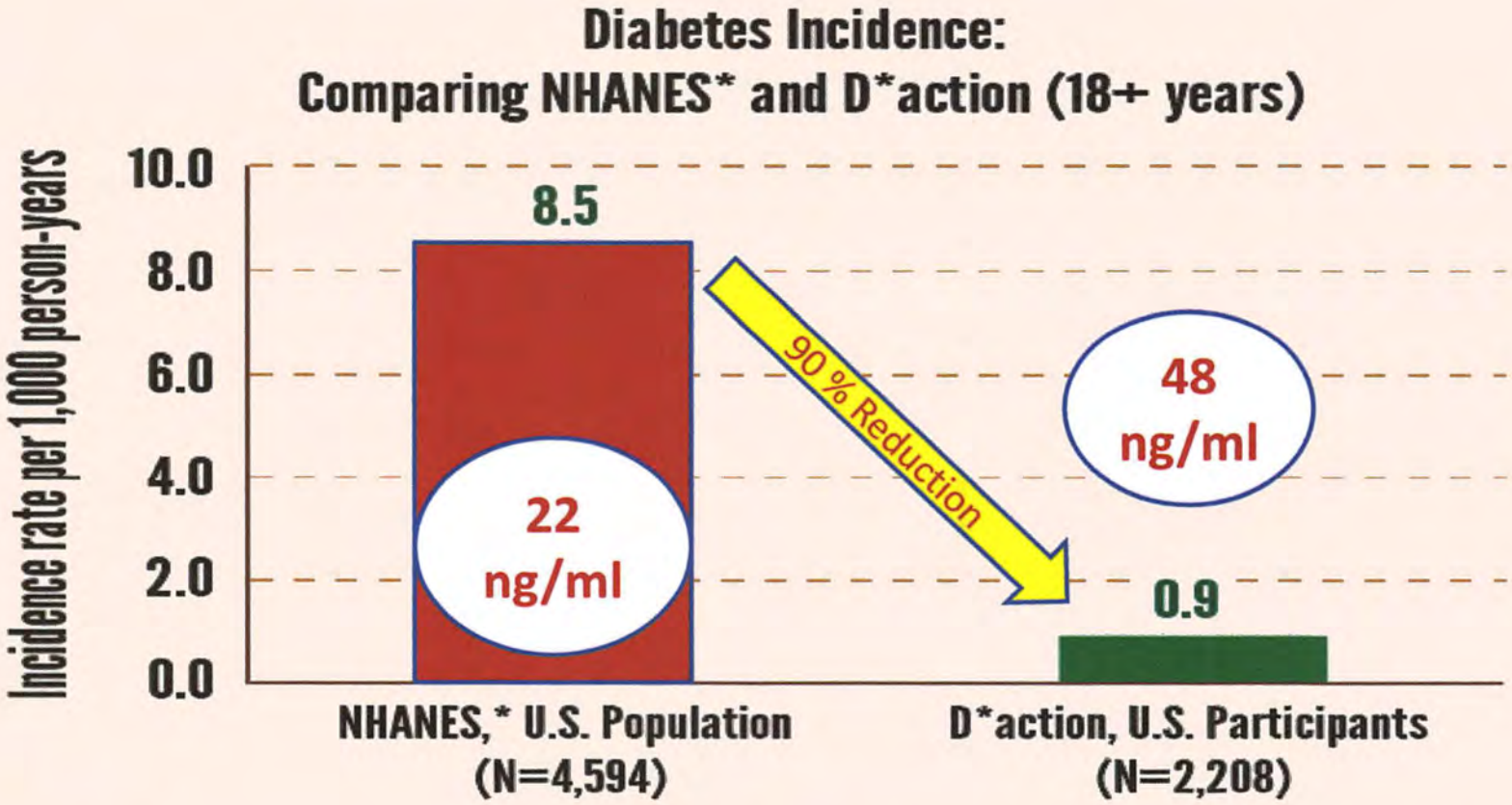
AK State Cost for Colorectal Cancer per year **$ 3,925,900**

50% per year savings with vitamin D

$1,962,950

(meta-analysis Gorham et. al.)

TYPE 2 DIABETES



Vitamin D*action

GrassrootsHealth
A Public Health Promotion Organization
www.grassrootshealth.net

*DATA SOURCE: NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES), 2005-2006

**RATE RATIO = 9.7 (P=0.0002)

(Notes by the office of Rep Seaton)

Chart Date 8/6/13

Preliminary data, not yet published.

Active State Of Alaska employees, Retirees and dependents – **83,000**

Employees, Retirees and dependents minus those with Diabetes already – **71,143**

New incidences of diabetes per year – **8.5 per 1,000 per year (.0085)**

Average cost of annual medical expenditures directly attributable to diabetes – **$7,900**

=

Current Diabetes Cost per year= **$4,777,252**

Per year Savings at 90% reduction = $4,299,527

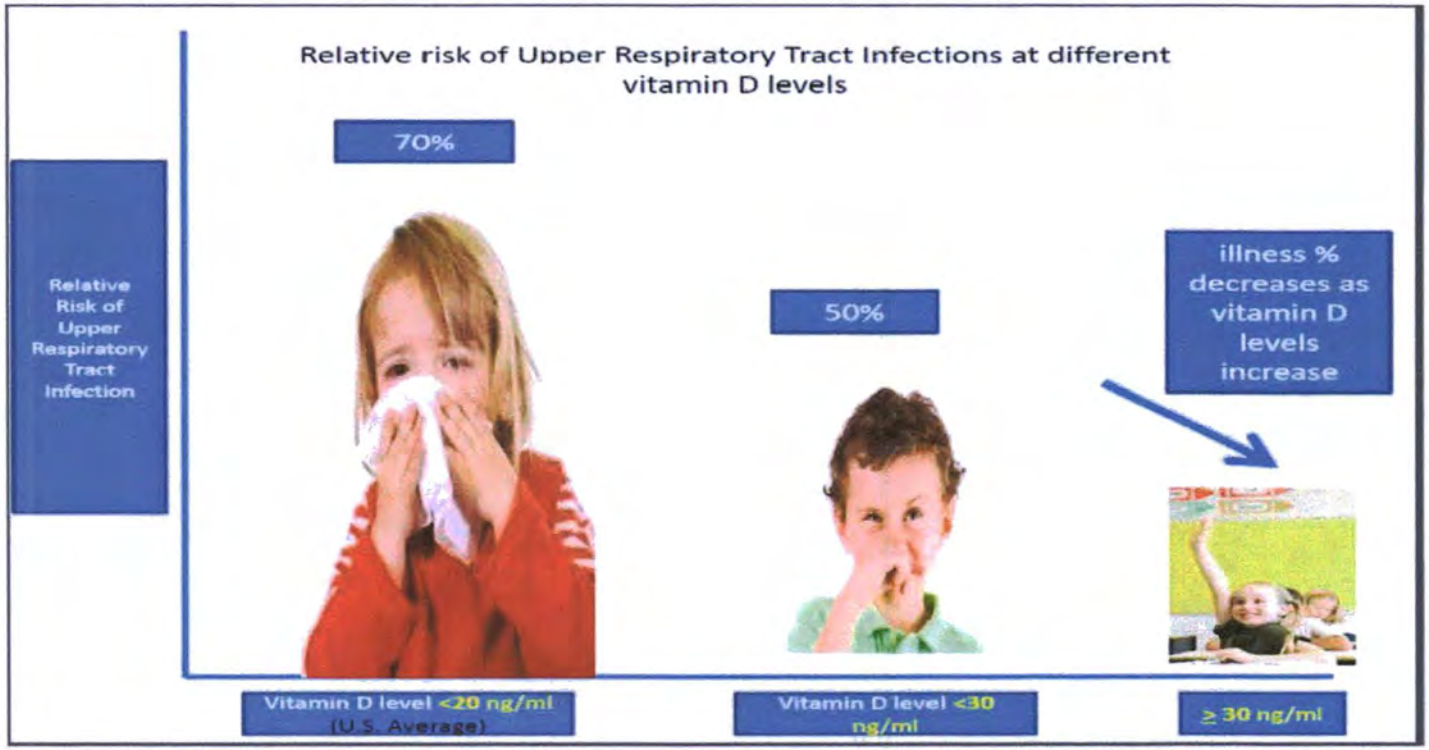
(GrassrootsHealth D*Action study)

Per year Savings at 38% reduction = $1,815,356

(Meta-analysis of prospective studies - Song et.al.)

Upper Respiratory Tract Infections

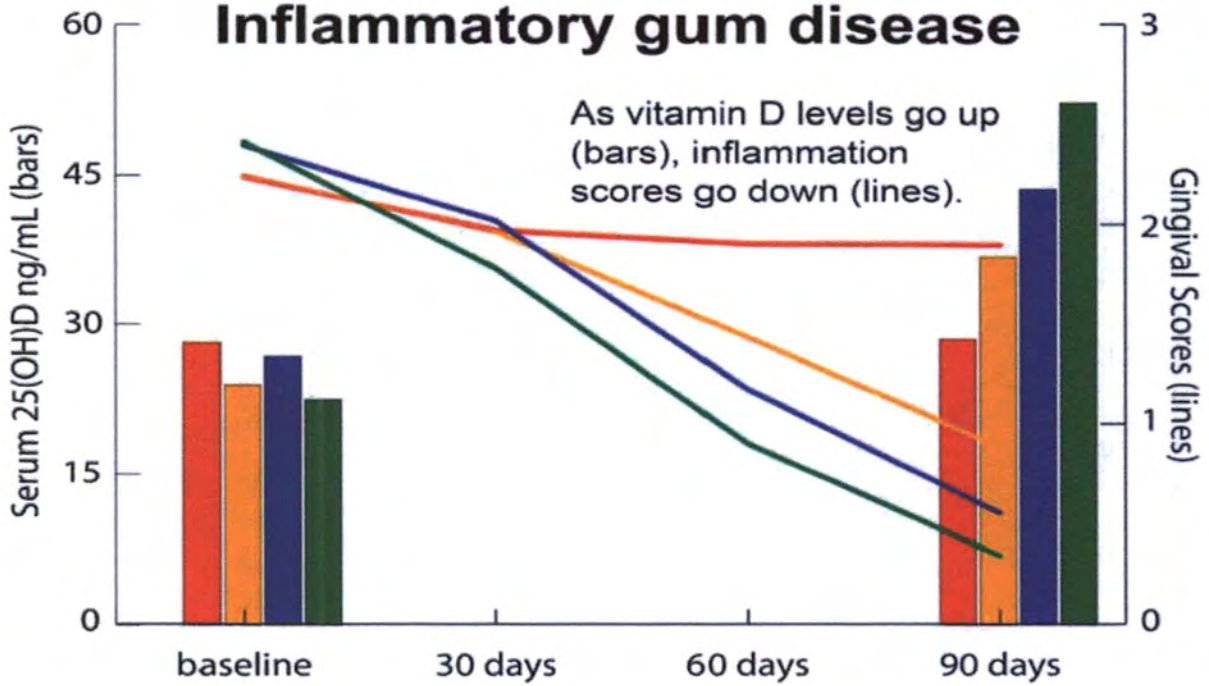
Recently, a study was conducted with seven hundred forty-three children ages 3-15 in a Canadian Hutterite Community. **The findings of the study show that children with higher vitamin D blood levels had a 50% lower relative risk of contracting an Upper Respiratory Tract infection.** Those children at the United States national average of 21 ng/ml vitamin D levels were at a 70% greater risk of contracting respiratory infections. Illnesses such as RTI's are commonly a factor in children's absences from school. Making sure your child has sufficient vitamin D will not only increase their health, but will lead to less school absences due to illness.



Low Serum 25 Hydroxyvitamin D level and Risk of Upper Respiratory tract infection in Children and Adolescents Science et. al. Journal of Clinical Infectious Diseases, August 2013 volume 57.

Prepared by the office of Representative Paul Seaton

Inflammatory gum disease



0 IU (placebo)	After 3 months
500 IU/day	More than 50% reduction
1000 IU/day	More than 65% reduction
2000 IU/day	More than 80% reduction

Hiremath VP, Rao CB, Naik V, Prasad KVV. Anti-inflammatory Effect of Vitamin D on Gingivitis: A Dose-Response Randomised Control Trial. Oral Health Prev. Dent. 2013; 11(1):61-69. (notes by Seaton)

CME AVAILABLE FOR THIS ARTICLE AT ACOEM.ORG

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

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

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

Learning Objectives

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

JOEM • Volume 54, Number 2, February 2012

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

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

Midwestern Health Care System Employees in Study = **10,646 workers**

Estimated Employer Health Care Costs Due to Diminished Employee Productivity from Illness = **15% to 73%, or more than $150 Billion Per Year**

Active State Employees: **17,338**

Estimated Savings for Above 20 ng/mL of Vit. D Compared to Below 20 ng/mL

= $112 Per Employee Per Year *or*
total of $1.9 Million Per Year

Estimated Savings for Above 40 ng/mL of Vit. D Compared to Below

= $370 Per Employee Per Year *or*
total of $6.4 Million Per Year

CS FOR HOUSE BILL NO. 39(HSS)

FOR AN ACT ENTITLED

"An Act establishing the Advisory Committee on Wellness; and relating to the administration of state group health insurance policies."

percent annually.

*** Sec. 2.** AS 39.30.090(a) is amended by adding a new paragraph to read:

(13) To the greatest extent legally and reasonably practicable, the Department of Administration shall work to hold the escalation of health care costs to less than two percent annually by administering policies of group health insurance obtained under this subsection in a manner that is likely to reduce the incidence of disease in the state's population and that facilitates implementation of the recommendations of the Advisory Committee on Wellness established under AS 39.30.093.

*** Sec. 3.** AS 39.30.091 is amended by adding a new subsection to read:

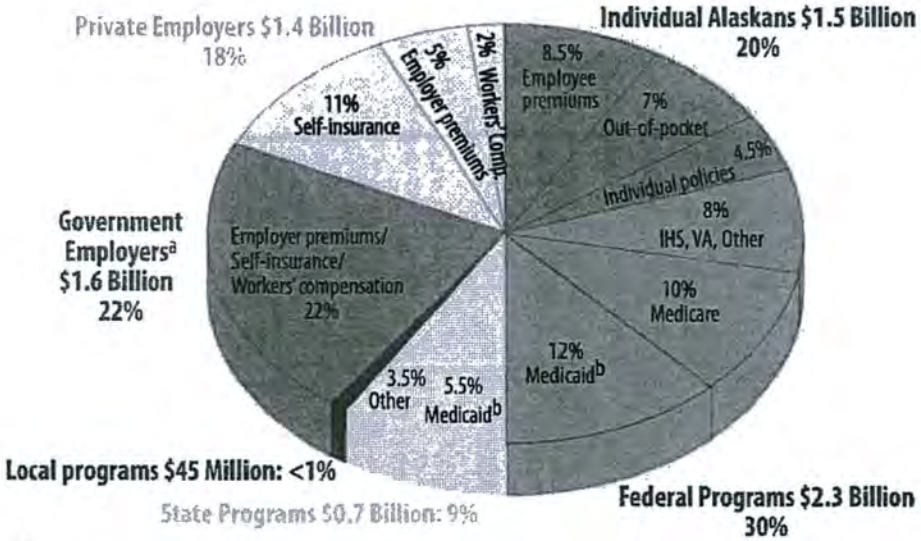
ALASKA HEALTHCARE COSTS

Alaska's Health-Care Bill: $7.5 Billion and Climbing

By Mark A. Foster and Scott Goldsmith

UA Research Summary No. 18 • August 2011
Institute of Social and Economic Research • University of Alaska Anchorage

Figure 1. Who Pays for Health Care in Alaska?
(2010 Spending: $7.5 Billion)



[a] Insufficient data to break out categories
[b] The federal and state governments share the cost of Medicaid.

Source: Authors' estimates

Health-care spending for Alaskans reached about $7.5 billion in 2010. For comparison, that's close to half the wellhead value of all the oil produced in Alaska that year. It's also roughly equal to half the wages Alaskans collected in 2010.

The state's health-care spending has been rising fast, tripling since 1990 and jumping 40% just between 2005 and 2010—and at current trends it could double by 2020, reaching more than $14 billion.

Here we report on who's paying the bills, what we're buying, what's contributing to the growth, and other aspects of health-care spending. We conclude with a discussion of how Alaska could get better value for its health-care dollars.

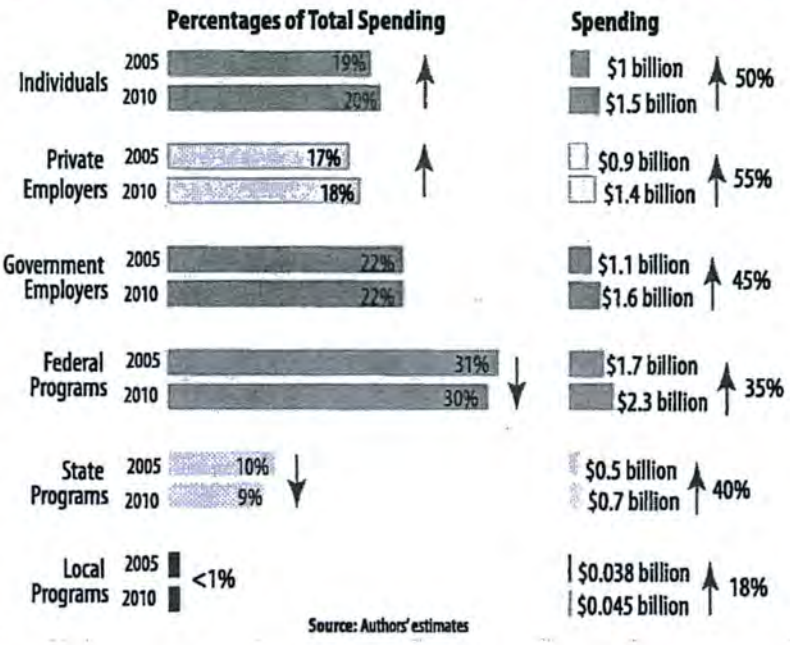
- ***Who pays the bills?*** Individual Alaskans directly pay about 20%, state and federal programs around 40%, and private and government employers another 40% (Figure 1 and page 2).
- ***What's the biggest cost?*** Medicaid is the largest single expense, making up nearly 18% of all Alaska health-care spending. But that's down from 20% of total spending in 2005. Why? Because spending for Medicaid didn't grow as fast as other kinds of spending (page 3).
- ***Are costs shifting?*** Every category of spending increased since 2005—but because spending by individuals and private employers increased faster, their shares of total spending increased (page 4).
- ***What are we buying?*** Hospitals and doctors account for nearly 60% of total spending—but the next largest cost is the 10% that goes for administering private and government health insurance (page 4).
- ***What's driving spending*** Over the past 50 years, technology, income growth, medical-price inflation, changing insurance coverage, and a growing, aging population have driven health-care spending (page 5).
- ***How many Alaskans are uninsured?*** The answer varies depending on how "uninsured" is measured and when. But recent estimates say about 18% of adults and 9% of children are uninsured. Based on 2010 census figures, that would be about 17,000 children and 94,000 adults (page 6).
- ***How many Alaska businesses offer health insurance?*** More than 90% of large firms offer insurance, compared with just 30% of small businesses—and that's down from 35% in 2003 (page 7).
- ***Are prices higher in Alaska?*** Yes. But Alaska's isolation, small markets, and other factors contribute to those higher prices—a day in the hospital costs on average 50% more than in the U.S. as a whole, and costs for common procedures are roughly 35% higher (page 8).
- ***How is spending distributed?*** Just 10% of Americans are responsible for two-thirds of all health-care spending in an average year (page 9).
- ***What about the future?*** Expanded insurance coverage; an aging population; and continued growth in technology, incomes, and medical prices will keep driving growth in health-care spending in the coming years. Controlling that growth will be an ongoing challenge (page 11).

How Have Patterns of Spending Changed?

Every category of health-care spending increased between 2005 and 2010, but the shares of spending shifted slightly among the various payers. We don't have enough information to say exactly what caused this shift—but several things likely contributed, as we describe below.

- *Individuals paid 20% of Alaska's health-care bills in 2010, up from 19% in 2005.* As costs of health-care benefits increased rapidly, employers shifted more of those costs to employees (see page 7). Also, prices for policies individuals buy directly increased significantly.
- *Private employers' share of spending increased from 17% to 18%.* That increase was in part because private industry added nearly four times more jobs than governments did since 2005—and at least some of that bigger base of employees had health-care coverage.
- *Government employers' share of spending was about the same, at 22%.*
- *Government health programs accounted for a somewhat smaller share of spending, down from about 41% to 39%.* The federal and state governments have attempted to hold down growth in costs of health programs—but federal programs alone continue to make up nearly a third of all Alaska's health-care spending. Local government spending for health programs remains small, relative to that of the state and federal governments, and the increase in local spending was smaller as well.

Figure 6. Changes in Who Pays for Alaska Health-Care, 2005-2010



Source: Authors' estimates

What Do Health-Care Dollars Buy?

Alaska's $7.5 billion health-care bill includes everything from visits to doctors and dentists to prescriptions and nursing-home care.[5] Figure 7 summarizes what Alaska's health-care dollars bought in 2010.

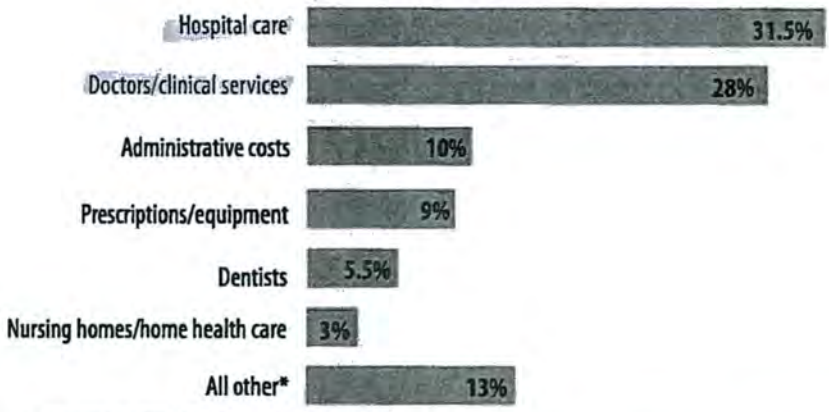
- *Hospital care was the largest expense,* followed closely by payments for doctors and related clinical services—together they accounted for about 60% of Alaska health-care spending in 2010.
- *Administering private and public insurance plans cost one of every ten dollars* spent for Alaska health care in 2010. That's more than spending for prescriptions and medical equipment, and nearly twice the spending for dentists.
- *Spending for nursing homes and home-health care made up only about 3%* of total spending, even though spending for home health care has increased rapidly in the past decade. Much of this care is paid for under Medicaid.

How About Health-Care Jobs?

This summary looks at health care from the perspective of spending for care—but it's important to remember that the spending also supports jobs for Alaskans. As the Alaska Department of Labor and Workforce Development reports in its August 2011 *Alaska Economic Trends*:

- Health-care spending directly supports 31,800 jobs in Alaska. That's one in ten of all wage and salary jobs—in hospitals, offices of doctors and other providers, nursing homes, and many other places.
- Many additional jobs related to health care—in government agencies, and among the self-employed—aren't included in that total.
- Alaska employment in health care has been increasing at an annual rate of 4.3% for the past decade.

Figure 7. What Do Alaska's Health-Care Dollars Buy?
(2010 Spending: $7.5 Billion)



*Other personal and professional care and public health activities.

Source: Mark A. Foster and Associates estimates, based on Centers for Medicare and Medicaid Services, National Health Expenditure accounts

Who Pays the Bills?

Individuals, private employers, and governments share the direct costs of health care in Alaska (Figure 1 and Table 1).

Individual Alaskans spent about $1.5 billion for health care in 2010—20% of total spending.

- *Alaskans with employer-based insurance—both private and government—paid about $640 million* for premiums, and those with individual policies spent $350 million.
- *Out-of-pocket costs for Alaskans totaled about $545 million* in 2010. That includes deductibles and co-pays—the part of medical bills insurance doesn't pay. It also includes costs for services not covered by insurance, and money that uninsured Alaskans spent for medical bills.

Private employers spent about $1.4 billion—18% of total spending.

- *Alaska businesses spent around $835 million to self-insure* in 2010. They set aside money to pay medical bills themselves, rather than pay insurance premiums. They're betting that the medical bills will be less than the premiums they would have paid—and that their reserves will be enough to cover annual variation in claims. Many self-insured firms carry "stop loss" insurance, to protect them against very large claims. At first only large firms self-insured, but as insurance costs climbed, smaller businesses have also begun self-insuring.
- *Businesses spent about $400 million for insurance premiums* in 2010. That's only about half what businesses spent to self-insure, showing how widespread the practice of self-insuring is.
- *Medical bills of employees injured at work cost businesses about $150 million* in 2010. State law requires employers to pay for such injuries.

Government employers spent $1.6 billion for health benefits in 2010.

- *Local government employers—including school districts—spent about $630 million*, the federal government nearly $590 million, and the state $410 million.
- *Like businesses, many public employers self-insure, rather than pay insurance premiums*—but we don't have enough data to separate out those costs. The federal government also pays medical costs for active-duty and retired military personnel and veterans.

Governments spent nearly $3 billion for health programs in 2010.

- *Medicaid spending was nearly $1.3 billion in 2010*—$871 million in federal money and $409 million in state money. Medicaid is a federal program, but the state administers it and shares the costs (see page 3).
- *Medicare spending was $733 million in 2010*, accounting for nearly 10% of all health-care spending. Medicare is a federal program for people 65 and older and those with certain disabilities. Medicare spending is expected to grow rapidly in the next decade, as older Alaskans make up an ever-growing share of the population (see page 5).
- *The federal government spent close to $650 million for other health programs* in 2010, including the Indian Health Service, which provides medical care for Alaska Natives, and the Veterans Administration, which provides care for military veterans. Spending for these programs depends somewhat on enrollment, but it's also constrained by Congressional appropriations.
- *Besides its share of Medicaid, the state government spent about $260 million* for a variety of other programs in 2010, including grants to local governments, the state-operated Pioneer Homes for older Alaskans, and the Alaska Psychiatric Institute.

Table 1. Health-Care Spending in Alaska, 2010
(Total Spending: $7.5 Billion)

Individuals	**$1,529 million**
Employee premiums	$637
Out-of-pocket costs	$544
Individual policies	$348
Private Employers*	**$1,384 million**
Insurance premiums	$395
Self-insurance costs	$836
Workers' compensation medical	$153
Government Employers*	**$1,625 million**
Federal	$586
State	$408
Local	$631
Federal Health Programs	**$2,250 million**
Medicare	$733
Medicaid	$871
IHS, VA, Community Health Centers, public health, K-12 health	$646
State Health Programs	**$670 million**
Medicaid	$409
Local grants, API, Pioneer Homes, K-12 health, WAMI, Department of Corrections	$261
Local Health Programs	**$45 million**
Hospital and health program support	$40
Other local	$5

*Includes coverage for current and retired employees.
Source: Authors' estimates. See page 12 for a description of what's included in health-care costs.

- *Local health programs are much smaller*, at around $45 million in 2010, largely support for hospitals and health programs.

And finally, keep in mind that even though governments and businesses pays most of the *direct* costs of health care, individual Alaskans and other Americans *indirectly* pay all the costs of health care—because they buy goods and services, own businesses, and pay taxes.

ALASKA ACTIVE AND RETIREE HEALTH PLAN DATA

HealthSmart
CARE MANAGEMENT SOLUTIONS

4th Quarter Report 2013

Aggregate Risk Profile

ACTIVE PLAN

Member Information			
Member Count	17338	Avg Forecasted Cost	$6,670
Avg Age	35	Avg Total Cost	$6,774
Percent Female	51%	Avg Forecasted Risk Index	1.09
Avg Months Enrolled	11	%/w Acute Impact Score >= 95	1.06%
		%/w Chronic Impact Score >= 95	5.38%
		%/w Motivation Rank >= 95	4.83%

Aggregate Risk Summary

Risk Drivers	# Members	Avg Risk Contribution		Contribution to Forecast	Risk Contribution	
Demographics	17338	SENIORS SKIN, FRACTURES, FALLS	$345	$5,987,784	5.18%	X
Acute Respiratory Disorders	2880	TUBERCULOSIS	$1,129	$3,251,578	2.81%	X
Arrhythmia Disorders	220		$3,382	$744,142	0.64%	
CHF Conditions	673	CHRONIC HEART FAILURE	$3,181	$2,140,732	1.85%	X
Cerebral Vascular Disorder	247		$4,199	$1,037,177	0.90%	
Chronic Respiratory Disorders	1728	UPPER RESPIRATORY TRACT	$2,318	$4,005,542	3.46%	X
Coronary Artery Related Conditions	1655	CORONARY HEART DISEASE	$2,958	$4,895,538	4.23%	X
Dermatological Disorder	3075		$1,272	$3,911,805	3.38%	
Diabetic Disorders	882	TYPE 1 AND TYPE 2	$5,932	$5,231,998	4.52%	X
Female Reproductive Conditions	341	PRETERM BIRTHS	$2,510	$856,045	0.74%	X
Gastrointestinal Disorders	2351	COLORECTAL CANCER	$2,011	$4,728,854	4.09%	X
Heart Related Conditions	180		$5,628	$1,013,046	0.88%	
Hypertension	1527	BLOOD PRESSURE	$1,983	$3,028,315	2.62%	X
Hypotensive Drugs	1784		$2,207	$3,937,924	3.41%	
Major Infection Related Conditions	2950	MRSA	$2,023	$5,968,497	5.16%	X
Metabolic Conditions	3077	FIBROMYALGIA	$2,680	$8,247,421	7.13%	X
Minor Infection Related Conditions	3704		$1,340	$4,965,037	4.29%	
Miscellaneous Conditions	4750		$2,303	$10,940,696	9.46%	
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Myocardial Infarction Related Conditions	271		$5,315	$1,440,328	1.25%	
Neonatal Issues	255	AUTISM, HEART PROGRAMMING	$935	$238,299	0.21%	X
Neoplastic Related Conditions	638		$4,332	$2,763,900	2.39%	
Neurological Disorder	3770	ALZHEIMER'S	$1,435	$5,409,047	4.68%	X
Non-specific condition	5561		$140	$780,877	0.68%	
Pneumonia	243	UPPER RESPIRATORY TRACT	$3,822	$928,744	0.80%	X
Psychological Disorder	2688	S.A.D. AND DEPRESSION	$2,771	$7,447,883	6.44%	X
Renal Disorders	309		$15,145	$4,679,794	4.05%	
Trauma Related Condition	1822	TRAUMATIC BRAIN INJURY	$1,455	$2,651,019	2.29%	X
Urinary Disorders	1381		$2,170	$2,996,360	2.59%	

% total diseases directly related to Vitamin D status = 66.08 %

Notes in red by office of Rep. Seaton

RETIREE PLAN

HealthSmart CARE MANAGEMENT SOLUTIONS

4th Quarter Report 2013

Aggregate Risk Profile

Member Information			
Member Count	65376	Avg Forecasted Cost	$15,666
Avg Age	63	Avg Total Cost	$17,726
Percent Female	54%	Avg Forecasted Risk Index	2.56
Avg Months Enrolled	12	%/w Acute Impact Score >= 95	5.47%
		%/w Chronic Impact Score >= 95	16.63%
		%/w Motivation Rank >= 95	9.70%

Aggregate Risk Summary

Risk Drivers	# Members	Avg Risk Contribution		Contribution to Forecast	Risk Contribution	
Demographics	65376	SENIORS SKIN, FRACTURES, FALLS	$454	$29,702,943	2.90%	X
Acute Respiratory Disorders	9520	TUBERCULOSIS	$1,669	$15,893,121	1.55%	X
Arrhythmia Disorders	5170		$2,860	$14,786,038	1.44%	
CHF Conditions	10658	CHRONIC HEART FAILURE	$2,758	$29,389,999	2.87%	X
Cerebral Vascular Disorder	5021		$3,726	$18,710,595	1.83%	
Chronic Respiratory Disorders	11241	UPPER RESPIRATORY TRACT	$3,093	$34,763,411	3.39%	X
Coronary Artery Related Conditions	24057	CORONARY HEART DISEASE	$2,900	$69,776,210	6.81%	X
Dermatological Disorder	15979		$1,958	$31,281,265	3.05%	
Diabetic Disorders	10689	TYPE 1 AND TYPE 2	$5,966	$63,771,119	6.23%	X
Female Reproductive Conditions	103	PRETERM BIRTHS	$1,489	$153,413	0.01%	X
Gastrointestinal Disorders	18753	COLORECTAL CANCER	$2,146	$40,246,314	3.93%	X
Heart Related Conditions	4346		$4,374	$19,007,254	1.86%	
Hypertension	21394	BLOOD PRESSURE	$1,623	$34,713,887	3.39%	X
Hypotensive Drugs	21282		$1,869	$39,772,355	3.88%	
Major Infection Related Conditions	13879	MRSA	$3,007	$41,731,745	4.07%	X
Metabolic Conditions	28763	FIBROMYALGIA	$2,545	$73,213,862	7.15%	X
Minor Infection Related Conditions	14339		$1,726	$24,754,410	2.42%	
Miscellaneous Conditions	32888		$2,762	$90,833,634	8.87%	
Musculo-skeletal Disorders	32886	INFANT MUSCLE, SENIOR FALLS	$2,498	$82,154,255	8.02%	X
Myocardial Infarction Related Conditions	5796		$3,424	$19,844,208	1.94%	
Neonatal Issues	63	AUTISM, HEART PROGRAMMING	$1,504	$94,751	0.01%	X
Neoplastic Related Conditions	7447		$3,928	$29,253,071	2.86%	
Neurological Disorder	27775	ALZHEIMER'S	$1,561	$43,366,164	4.23%	X
Non-specific condition	12687		$113	$1,429,752	0.14%	
Pneumonia	1619	UPPER RESPIRATORY TRACT	$5,098	$8,254,358	0.81%	X
Psychological Disorder	16031	S.A.D. AND DEPRESSION	$2,659	$42,623,390	4.16%	X
Renal Disorders	4750		$16,668	$79,174,484	7.73%	
Trauma Related Condition	8749	TRAUMATIC BRAIN INJURY	$1,904	$16,660,268	1.63%	X
Urinary Disorders	11515		$2,504	$28,836,425	2.82%	

% total diseases directly related to Vitamin D status = 61.16%

Notes in red by office of Rep. Seaton

Seaton Background Documentation 7

PRODUCTIVITY AT WORK

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

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

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

Learning Objectives

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

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

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

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

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

METHODS

Participants

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

Measures

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

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

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

Authors Plotnikoff, Finch, and Dusek, received support for this research by the Allina Hospitals and Clinics Employee Benefits Office, the Allina Center for Healthcare Innovation and Diasorin, Inc. Author Plotnikoff has consulted for Diasorin, Inc.

Diasorin Inc. had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, or the preparation or approval of the manuscript.

The JOEM Editorial Board and planners have no financial interest related to this research.

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DOI: 10.1097/JOM.0b013e318240df1e

Midwestern Health Care System Employees in Study = **10,646 workers**

Estimated Employer Health Care Costs Due to Diminished Employee Productivity from Illness = **15% to 73%, or more than $150 Billion Per Year**

Active State Employees: **17,338**

Estimated Savings for Above 20 ng/mL of Vit. D Compared to Below 20 ng/mL

= $112 Per Employee Per Year *or* total of $1.9 Million Per Year

Estimated Savings for Above 40 ng/mL of Vit. D Compared to Below

= $370 Per Employee Per Year *or* total of $6.4 Million Per Year

ECONOMIC BURDENS TO THE U.S. DUE TO INSUFFICIENT SOLAR ULTRAVIOLET IRRADIANCE

Photochemistry and Photobiology, 2005, 81: 1276–1286

Symposium-in-Print
UV Radiation, Vitamin D and Human Health: An Unfolding Controversy

Comparisons of Estimated Economic Burdens due to Insufficient Solar Ultraviolet Irradiance and Vitamin D and Excess Solar UV Irradiance for the United States

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ABSTRACT

Vitamin D sufficiency is required for optimal health, and solar ultraviolet B (UVB) irradiance is an important source of vitamin D. UVB and/or vitamin D have been found in observational studies to be associated with reduced risk for over a dozen forms of cancer, multiple sclerosis, osteoporotic fractures, and several other diseases. On the other hand, excess UV irradiance is associated with adverse health outcomes such as cataracts, melanoma, and nonmelanoma skin cancer. Ecologic analyses are used to estimate the fraction of cancer mortality, multiple sclerosis prevalence, and cataract formation that can be prevented or delayed. Estimates from the literature are used for other diseases attributed to excess UV irradiation, additional cancer estimates, and osteoporotic fractures. These results are used to estimate the economic burdens of insufficient UVB irradiation and vitamin D insufficiency as well as excess UV irradiation in the United States for these diseases and conditions. We estimate that 50 000–63 000 individuals in the United States and 19 000–25 000 in the UK die prematurely from cancer annually due to insufficient vitamin D. The U.S. economic burden due to vitamin D insufficiency from inadequate exposure to solar UVB irradiance, diet, and supplements was estimated at $40–56 billion in 2004, whereas the economic burden for excess UV irradiance was estimated at $6–7 billion. These results suggest that increased vitamin D through UVB irradiance, fortification of food, and supplementation could reduce the health care burden in the United States, UK, and elsewhere. Further research is required to confirm these estimates.

INTRODUCTION

There is rapidly mounting evidence that vitamin D has many important health benefits and that adequate serum levels of 25-hydroxyvitamin D (25(OH)D) are required for optimal health (1–12). There are also studies indicating that solar ultraviolet B (UVB) exposure is the primary source of vitamin D for most people outside the near-polar regions (13). However, despite this evidence, public health leaders have been slow to accept the role of solar UVB irradiance and vitamin D in maintaining optimal health, in part, because of widespread concern regarding the risk of cutaneous malignant melanoma (CMM) and nonmelanoma skin cancer (NMSC) due to solar UV irradiance.

In this study, we estimate the economic burden of insufficient solar UVB irradiance and vitamin D in the United States and compare this estimate with the economic burden from excess UV irradiation over either short (sunburning) or long periods. The approach is to consider diseases for which a strong geographic variation in the United States can be identified for disease outcome and to then use these variations to estimate the fraction of the disease burden in the United States that can be attributed to insufficient UVB irradiance and/or vitamin D or to excess solar UV irradiance. For some diseases that are linked to vitamin D deficiency but for which geographical variations are not apparent within the United States, results in the literature are used. Following that, the results for the United States are extrapolated to the United Kingdom.

MATERIALS AND METHODS

The diseases for which economic burdens due to insufficient solar UVB irradiance and/or vitamin D are estimated are cancer, multiple sclerosis

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Abbreviations: B, billion (10^9); CMM, cutaneous malignant melanoma; KC, Korean Conflict; M, million (10^6); MR, mortality rates; MS, multiple sclerosis; NMSC, nonmelanoma skin cancer; RR, risk reduction; SPF, sun protection factor; SUNARC, Sunlight, Nutrition and Health Research Center; Th1, T helper cells 1; UVA, ultraviolet A (315–400 nm); UVB, ultraviolet B (290–315 nm); UVR, ultraviolet radiation (290–400 nm); VDR, vitamin D receptors; WWII, World War II; $1,25(OH)_2D_3$, 1,25-dihydroxy vitamin D_3; 25(OH)D, 25-hydroxyvitamin D.

2004 Estimated US Economic Burden Due to Vitamin D Insufficiency from Solar UVB Irradiance and Vit. D Intake = **$40 - $56 Billion**

2004 Estimated US Economic Burden Due to Excess UV Irradiance = **$6 - $7 Billion**

Estimated Per Year Savings with Sufficient Vitamin D for the United States

= $34 - $49 Billion

BENEFITS OF VITAMIN D FOR GERMANY

 DOI 10.1002/mnfr.200900494 *Mol. Nutr. Food Res.* 2010, *54*, 1164–1171

REVIEW

The estimated benefits of vitamin D for Germany

A. Zittermann

Clinic for Thoracic and Cardiovascular Surgery, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany

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

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Keywords:
Costs / Mortality / Survival / Ultraviolet radiation / Vitamin D

1 Introduction

Vitamin D is well known for its effects on calcium and bone metabolism. Vitamin D deficiency results in rickets in infants and small children and in osteomalacia and osteoporosis in adults. However, it is becoming increasingly clear that vitamin D has a much broader range of actions in the human body than believed before. The vitamin D receptor is nearly ubiquitously expressed, and almost all cells respond to vitamin D exposure; about 3% of the human genome is regulated, directly and/or indirectly, by the vitamin D endocrine system [1]. Consequently, vitamin D influences many physiological processes, including muscle function, cardiovascular homeostasis, nervous function, cellular integrity, and the immune response [2]. It is easy to imagine that severe disturbances in these biological systems have serious health effects. The present article gives an overview of the vitamin D status in Germany, provides evidence for an independent association of vitamin D deficiency with chronic diseases, and discusses preventive measures for improving vitamin D status in Germany.

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Abbreviation: RCT, randomized controlled trial

2 Vitamin D metabolism

Solar UVB radiation (290–315 nm) is the major source of vitamin D for humans, whereas dietary vitamin D is a second, less important source. Already, 20 min of a daily whole body exposure to UVB radiation trice a week is able to maintain adequate vitamin D status in people with light skin [3]. However, increased skin pigment can increase exposure time by factor six to achieve a similar effect [4]. Unfortunately, Germany has only a moderate climate and its geographic location (47°16'N to 55°04'N) is relatively northern. Generally, solar UV-B radiation is assumed to be negligible at geographic latitude of 40°N from November until February and at latitude of 50°N from October until April [5].

The UV-index for Rinteln, a small town in Central Germany (geographic latitude: 52°N), is illustrated in Fig. 1

German Population of **82 Million**

Estimated 38 Billion € Saved Annually

HOWEVER;

Assumption: Estimated 20,000 individuals survive premature death annually due to Vit. D intake, each individual would receive pension of 20,000€ annually.

Reduction of 0.5 Billion €

Total Annual Cost Savings in Germany by Improving Vitamin D to 100 nmol/L (42 ng/mL)

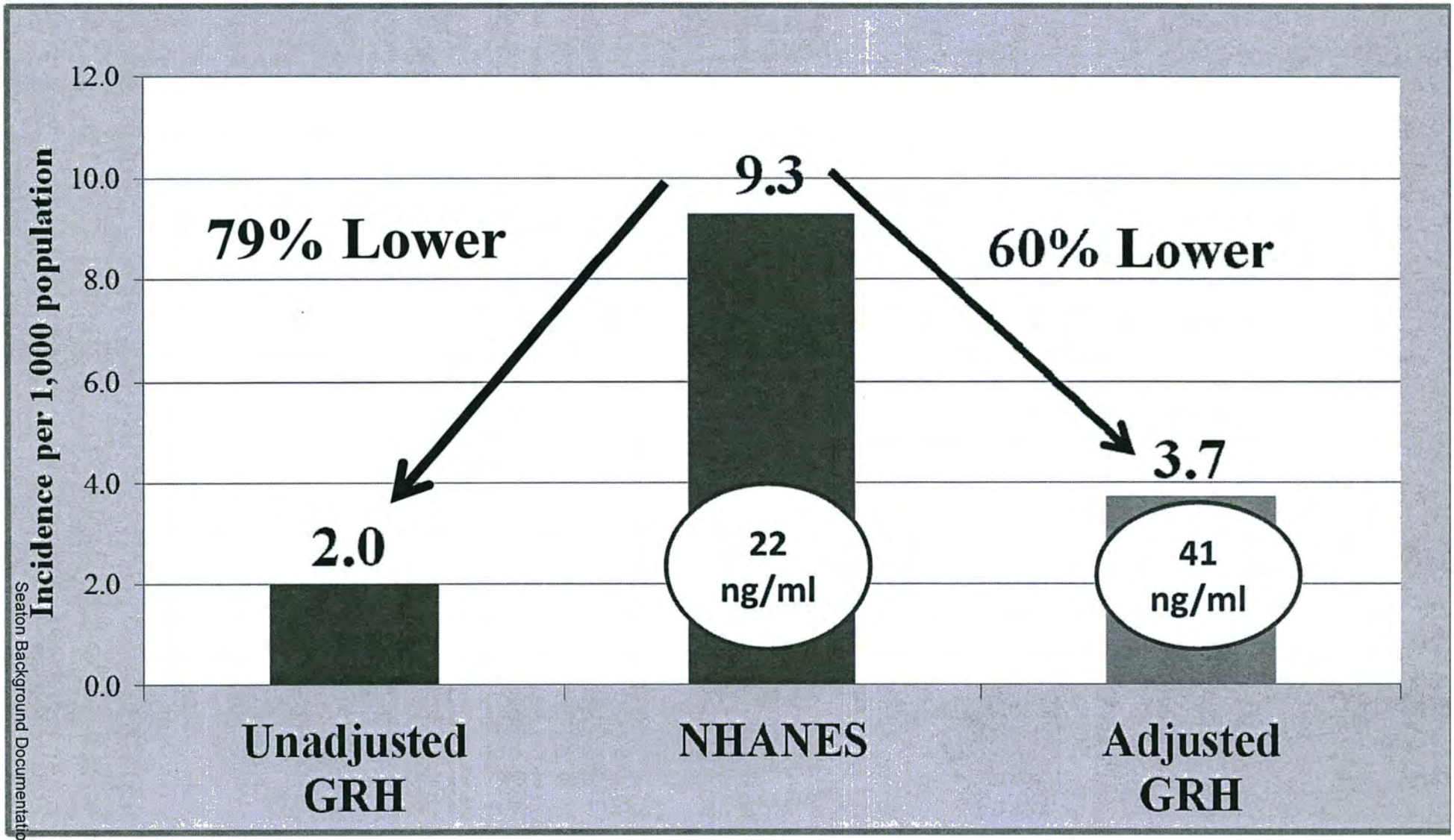
= 37.5 Billion €

Or

€ 457 per person

DIABETES COST

Type 2 Diabetes Incidence in GrassrootsHealth (N=4,933) and NHANES (N=4,078) Cohorts (age 20 and above)



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Median 25 (OH)D concentration in GRH cohort was 41 ng/ml and in NHANES was 22 ng/ml

(Notes by Rep Seaton)

Diabetes Care. 2013 May; 36(5):1422-8

Full text available at http://care.diabetesjournals.org/content/36/5/1422.full

Blood 25-Hydroxy Vitamin D Levels and Incident Type 2 Diabetes

A meta-analysis of prospective studies

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4. Liana C. Del Gobbo, PHD[3],
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Next Section

Abstract

OBJECTIVE To quantitatively assess the strength and shape of the association between blood 25-hydroxy vitamin D [25(OH)D] levels and incident risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS A systematic search of the MEDLINE and Embase databases and a hand search of references from original reports were conducted up to 31 October 2012. Prospective observational studies that assessed the association between blood levels of 25(OH)D and risk of incident type 2 diabetes were included for meta-analysis. DerSimonian and Laird's random-effects model was used. A quadratic spline regression analysis was used to examine the shape of the association with a generalized least-squares trend test performed for the dose-response relation.

RESULTS A total of 21 prospective studies involving 76,220 participants and 4,996 incident type 2 diabetes cases were included for meta-analysis. Comparing the highest to the lowest category of 25(OH)D levels, the summary relative risk for type 2 diabetes was 0.62 (95% CI 0.54–0.70). A spline regression model showed that higher 25(OH)D

38% Lower Risk of Type 2 with higher vitamin D

Active State Of Alaska employees, Retirees and dependents – **83,000**

Employees, Retirees and dependents minus those with Diabetes already – **71,143**

New incidences of diabetes per year – **8.5 per 1,000 per year (.0085)**

Average cost of annual medical expenditures directly attributable to diabetes – **$7,900**

=

Current Diabetes Cost per year= **$4,777,252**

Per year Savings at 90% reduction = $4,299,527

(GrassrootsHealth D*Action study)

Per year Savings at 38% reduction = $1,815,356

(Meta-analysis of prospective studies - Song et.al.)

COLORECTAL CANCER

VOLUME 29 · NUMBER 28 · OCTOBER 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Association Between Vitamin D and Risk of Colorectal Cancer: A Systematic Review of Prospective Studies

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Y.M. and H.Q. contributed equally to this work.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2928-3775/$20.00

DOI: 10.1200/JCO.2011.35.7566

ABSTRACT

Purpose
To conduct a systematic review of prospective studies assessing the association of vitamin D intake or blood levels of 25-hydroxyvitamin D [25(OH)D] with the risk of colorectal cancer using meta-analysis.

Methods
Relevant studies were identified by a search of MEDLINE and EMBASE databases before October 2010 with no restrictions. We included prospective studies that reported relative risk (RR) estimates with 95% CIs for the association between vitamin D intake or blood 25(OH)D levels and the risk of colorectal, colon, or rectal cancer. Approximately 1,000,000 participants from several countries were included in this analysis.

Results
Nine studies on vitamin D intake and nine studies on blood 25(OH)D levels were included in the meta-analysis. The pooled RRs of colorectal cancer for the highest versus lowest categories of vitamin D intake and blood 25(OH)D levels were 0.88 (95% CI, 0.80 to 0.96) and 0.67 (95% CI, 0.54 to 0.80), respectively. There was no heterogeneity among studies of vitamin D intake ($P = .19$) or among studies of blood 25(OH)D levels ($P = .96$). A 10 ng/mL increment in blood 25(OH)D level conferred an RR of 0.74 (95% CI, 0.63 to 0.89).

Conclusion
Vitamin D intake and blood 25(OH)D levels were inversely associated with the risk of colorectal cancer in this meta-analysis. 33% Lower Risk

J Clin Oncol 29:3775-3782. © 2011 by American Society of Clinical Oncology

INTRODUCTION

25-hydroxyvitamin D [25(OH)D] is the precursor of the physiologically active form of vitamin D. The serum level of 25(OH)D is a result of exposure of the skin to sunlight, total vitamin D intake, and other factors such as age and skin pigmentation.[1-2] Vitamin D has the ability to inhibit cell proliferation and increase apoptosis in vitro, and several tissues can locally produce the physiologically active form of vitamin D, which has anticarcinogenic properties.[3-6] In addition, many cell types, including colorectal epithelial cells, contain vitamin D receptors. These cells are able to convert the circulating 25(OH)D into active 1 to 25(OH)D metabolites, which in turn bind to the cells' own vitamin D receptors to produce an autocrine effect by inducing cell differentiation and inhibiting proliferation, invasiveness, angiogenesis, and metastatic potential.[7] Therefore, low vitamin D levels may increase the risk of colorectal cancer through the above potential mechanism. Currently, vitamin D deficiency is an important health problem in the industrial world[8-9]; in the United States, 25% to 58% of adolescents and adults are deficient in vitamin D.[10]

The results from prospective studies that have examined the association between vitamin D intake or 25(OH)D levels in the blood and the risk of colorectal cancer have been inconsistent. The aim of this review was to evaluate the evidence from prospective studies on vitamin D intake or blood levels of 25(OH)D and the risk of colorectal cancer by summarizing it quantitatively with a meta-analysis approach.

METHODS

Search Strategy

The literature search was conducted before October 2010 in the MEDLINE and EMBASE databases without restrictions and included articles ahead of publication. The following keywords were used in searching: "vitamin D or 25(OH)D" and "colorectal cancer or colon cancer or rectal cancer." Moreover, we searched

NOTE: Colorectal Cancer death rates in the Alaska Native community are nearly double the Alaska and U.S. Baseline population - Healthy Alaskans 2010 - DHSS

Optimal Vitamin D Status for Colorectal Cancer Prevention: A Quantitative Meta-Analysis
Edward D. Gorham, MPH, et. al. Am J Prev Med 2007;32(3)

Meta-analysis

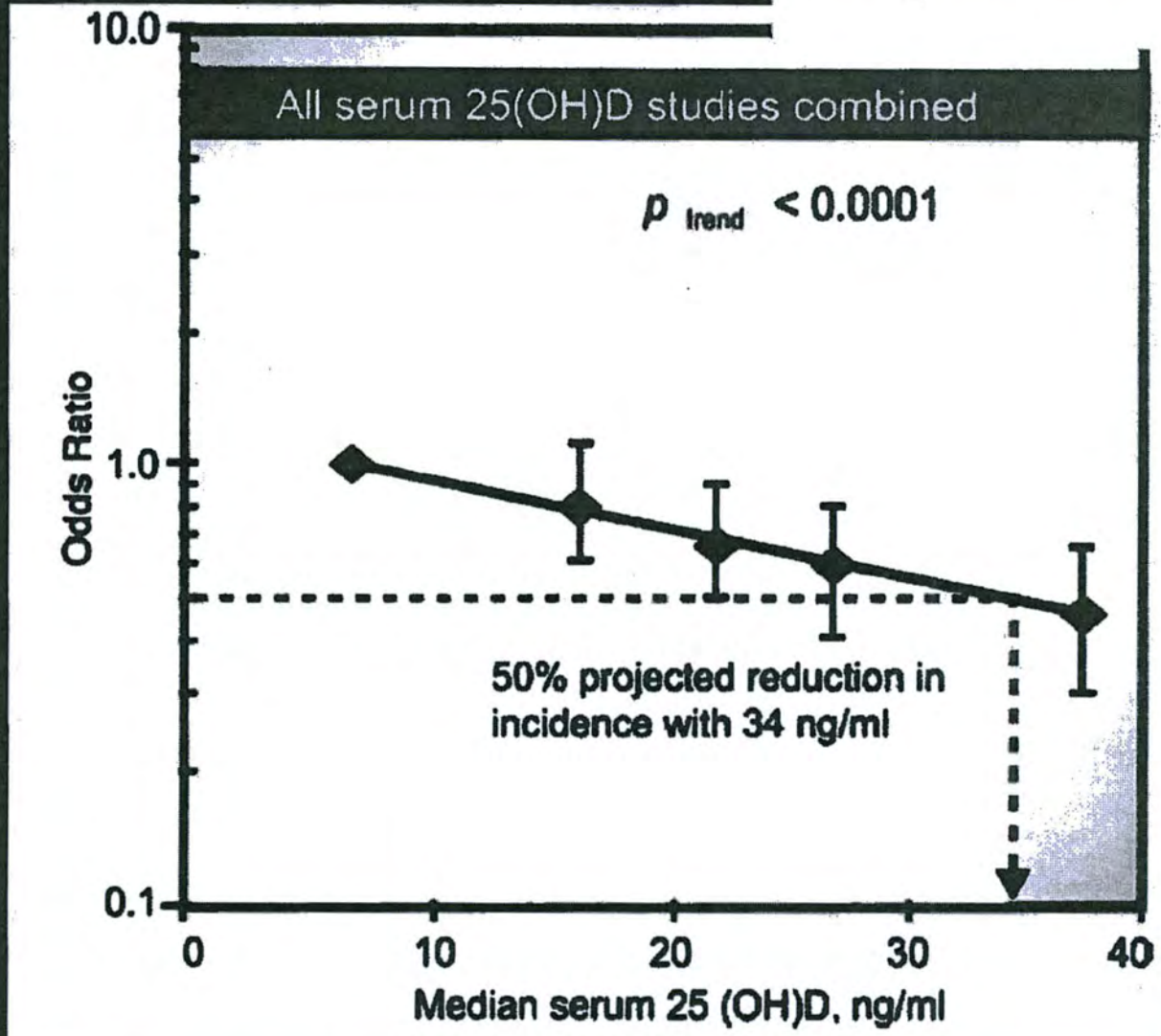


Figure 1. Dose–response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined.[1,4–7] The five points are the odds ratios for each quintile of 25(OH)D based on combined data from the five studies.

Active State Of Alaska employees, Retirees and dependents – **83,000**

Incidence of Colorectal Cancer per year in AK - **43 per 100,000 (.0043)**

Average cost of annual medical expenditures directly attributable to Colon Cancer – **$11,000**

=

AK State Cost for Colorectal Cancer per year **$ 3,925,900**

50% per year savings with vitamin D

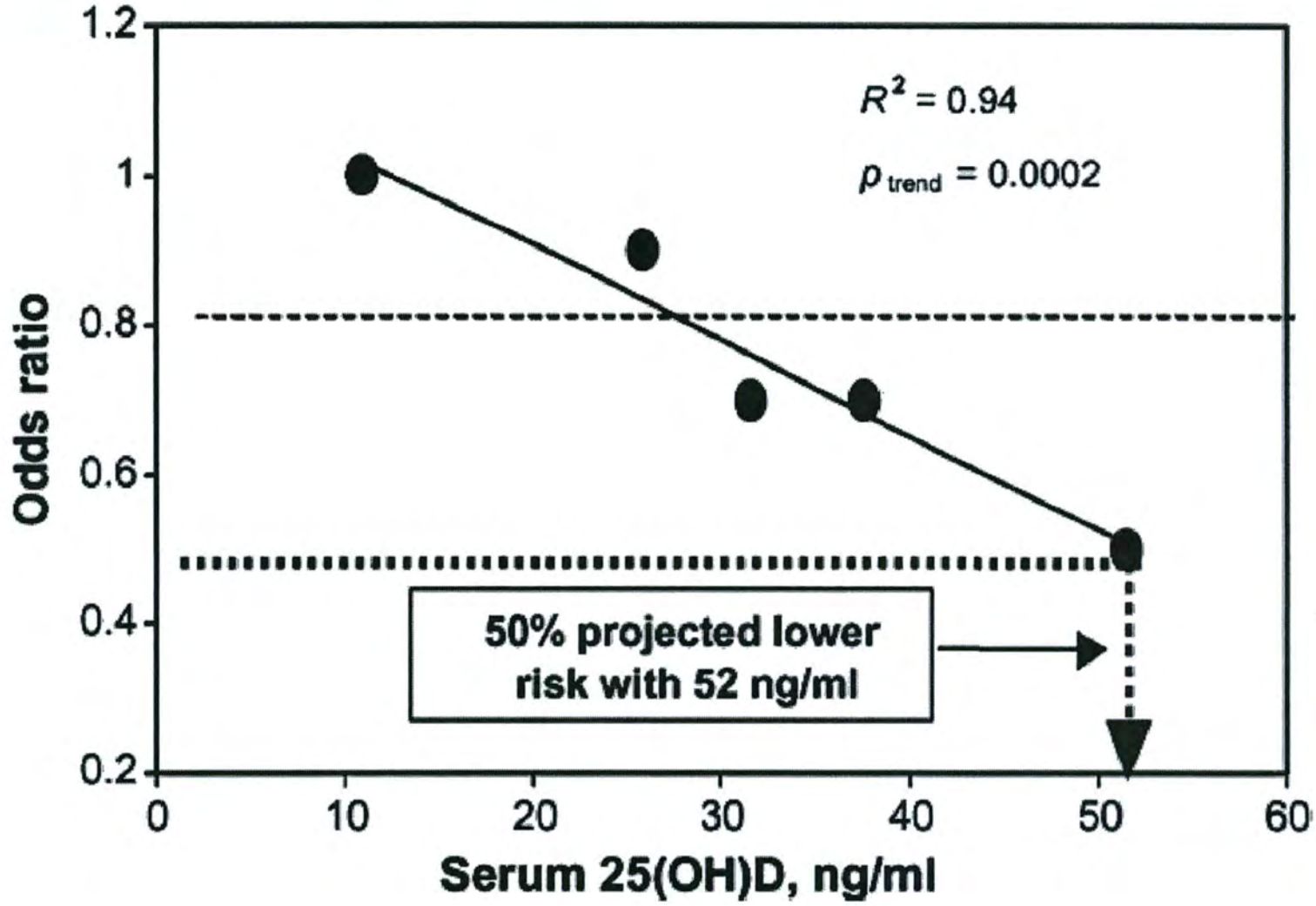
$1,962,950

(meta-analysis Gorham et. al.)

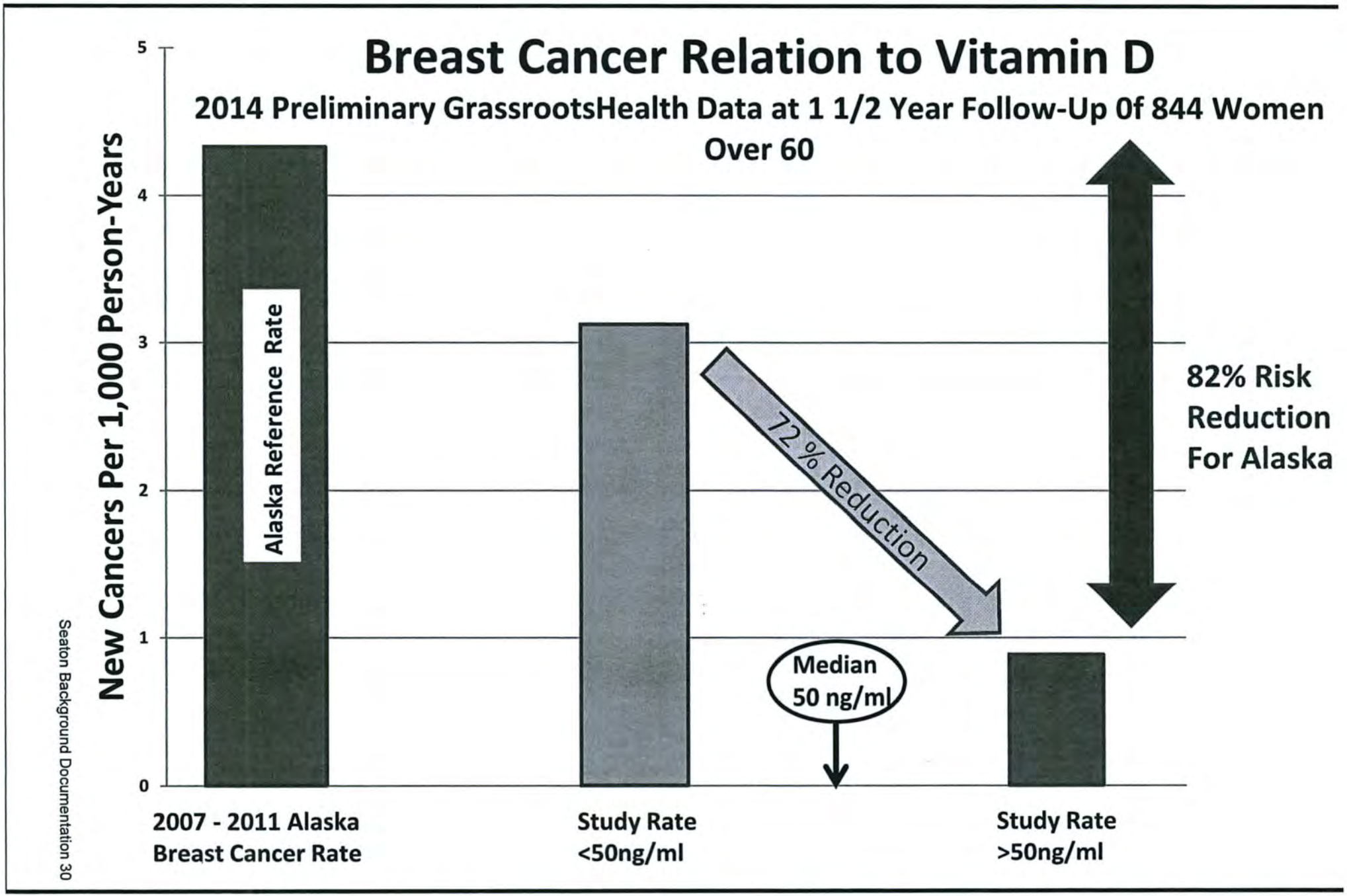
BREAST CANCER

Meta-analysis of breast cancer risk

[Slide by Cedric F. Garland, et al. University of California San Diego]



Dose–response gradient of risk of breast cancer according to serum 25-hydroxyvitamin D concentration, pooled analysis.



Hazard ratio of breast cancer for those with serum 25(OH)D <50ng/ml was 5.1 times more compared to those with ≥ 50ng/ml, adjusting for age and BMI. Chart arranged by the office of Representative Seaton

Active State Of Alaska employees, Retirees and dependents - **83,000**

Female percentage of AK employees and retirees: 53% = 43,990

Incidence of Breast Cancer per year in AK - **125 per 100,000 (.0125)**

Average cost of annual medical expenditures directly attributable to Breast Cancer - **$11,000**

=

Per year AK State Cost for Breast Cancer: $**6,048,625**

50% reduction with vitamin D
Per Year Savings with vitamin D:

$3,024,312

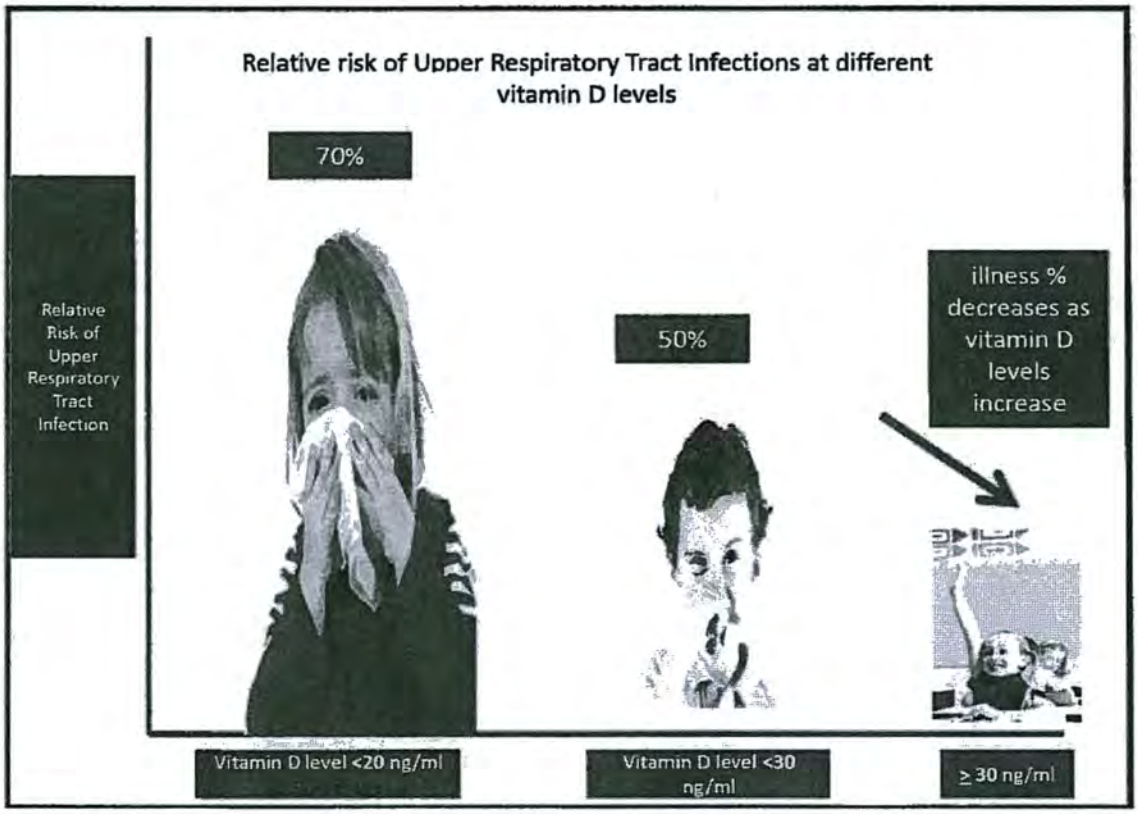
72% reduction with vitamin D (2014 GRH study)
Per Year Savings with Vitamin D:

$4,355,010

UPPER RESPIRATORY TRACT INFECTIONS

Upper Respiratory Tract Infections

Recently, a study was conducted with seven hundred forty-three children ages 3-15 in a Canadian Hutterite Community. **The findings of the study show that children with higher vitamin D blood levels had a 50% lower relative risk of contracting an Upper Respiratory Tract infection.** Those children at the United States national average of 21 ng/ml vitamin D levels were at a 70% greater risk of contracting respiratory infections. Illnesses such as RTI's are commonly a factor in children's absences from school. Making sure your child has sufficient vitamin D will not only increase their health, but will lead to less school absences due to illness.



Low Serum 25 Hydroxyvitamin D level and Risk of Upper Respiratory tract infection in Children and Adolescents **Science et. al. Journal of Clinical Infectious Diseases, August 2013 volume 57.**

Prepared by the office of Representative Paul Seaton

BMJ open
accessible medical research

Vitamin D_3 supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study

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ABSTRACT

Background: Low serum levels of 25-hydroxyvitamin D_3 are associated with an increased risk of respiratory tract infections (RTIs). Clinical trials with vitamin D_3 against various infections have been carried out but data are so far not conclusive. Thus, there is a need for additional randomised controlled trials of effects of vitamin D_3 on infections.

Objective: To investigate if supplementation with vitamin D_3 could reduce infectious symptoms and antibiotic consumption among patients with antibody deficiency or frequent RTIs.

Design: A double-blind randomised controlled trial.

Setting: Karolinska University Hospital, Huddinge.

Participants: 140 patients with antibody deficiency (selective IgA subclass deficiency, IgG subclass deficiency, common variable immune disorder) and patients with increased susceptibility to RTIs (>4 bacterial RTIs/year) but without immunological diagnosis.

Intervention: Vitamin D_3 (4000 IU) or placebo was given daily for 1 year.

Primary and secondary outcome measures: The primary endpoint was an infectious score based on five parameters: symptoms from respiratory tract, ears and sinuses, malaise and antibiotic consumption. Secondary endpoints were serum levels of 25-hydroxyvitamin D_3, microbiological findings and levels of antimicrobial peptides (LL-37, HNP1–3) in nasal fluid.

Results: The overall infectious score was significantly reduced for patients allocated to the vitamin D group (202 points) compared with the placebo group (249 points; adjusted relative score 0.771, 95% CI 0.604 to 0.985, p=0.04).

Limitations: A single study centre, small sample size and a selected group of patients. The sample size calculation was performed using p=0.02 as the significance level whereas the primary and secondary endpoints were analysed using the conventional p=0.05 as the significance level.

Conclusions: Supplementation with vitamin D_3 may reduce disease burden in patients with frequent RTIs.

ARTICLE SUMMARY

Article focus

- Recent evidence suggests that vitamin D_3 has potent extraskeletal effects, such as suppression of inflammation and strengthening of mucosal immunity by induction of antimicrobial peptides.
- Data from observational studies suggest that low levels of 25-hydroxyvitamin D_3 are associated with an increased risk of respiratory tract infections.
- Results from a limited number of randomised controlled trials on the protective role of vitamin D_3 against respiratory tract infections are inconclusive and thus additional studies are warranted.

Key messages

- Therefore we designed and carried out a randomised controlled trial where a large dose (4000 IU) of vitamin D_3 was given to patients with an increased susceptibility to infections for 1 year.
- The main conclusion is that vitamin D_3 supplementation reduces symptoms and antibiotic consumption among patients with an increased frequency of respiratory tract infections. Thus, vitamin D_3 supplementation may be an alternative strategy to reduce antibiotic use among patients with recurrent respiratory tract infections.

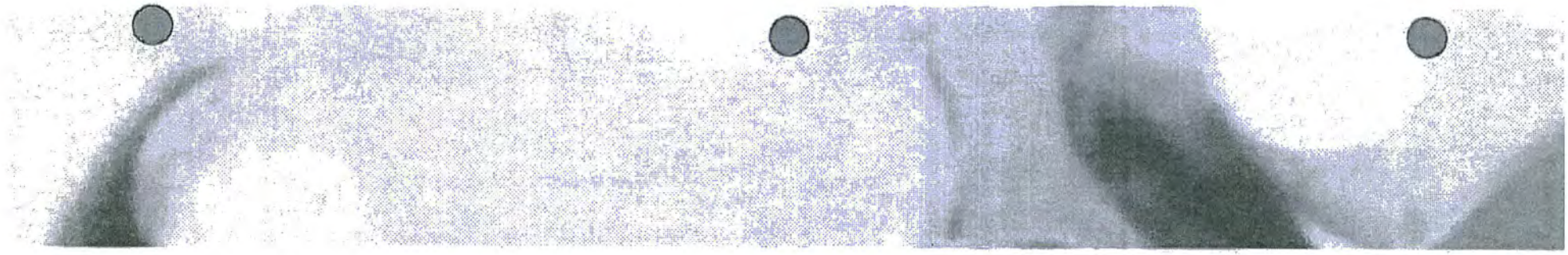
Strengths and limitations of this study

- A high daily dose of vitamin D_3 was used, the study time was a full year covering all seasons and patients with an increased frequency of respiratory tract infections were studied.
- A single study centre, small sample size (n=140) and a selected group of patients.

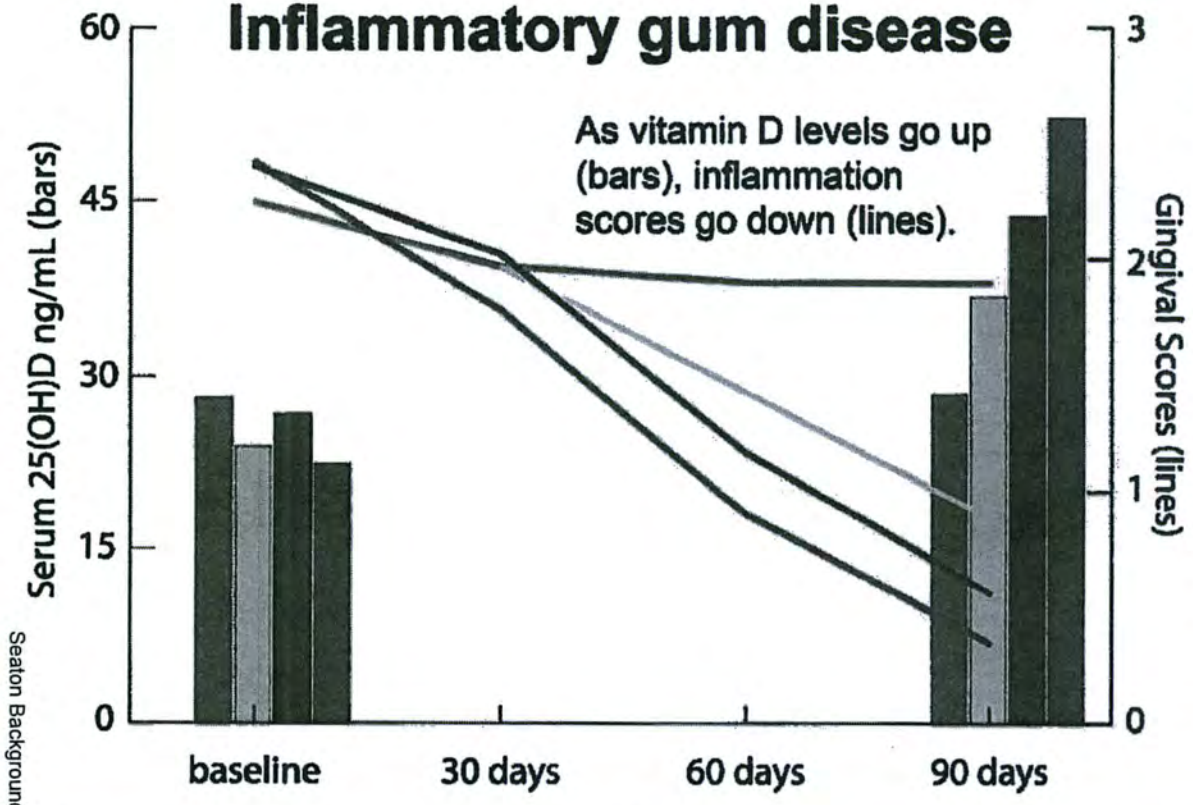
INTRODUCTION

Vitamin D was discovered when it was noted that rachitic children were improved by exposure to sunlight.[1] It was later shown by Holick *et al*[2] that vitamin D_3 is synthesised in the skin under the influence of ultraviolet light. Vitamin D_3 is further hydroxylated in the liver

INFLAMMATION



Inflammatory gum disease



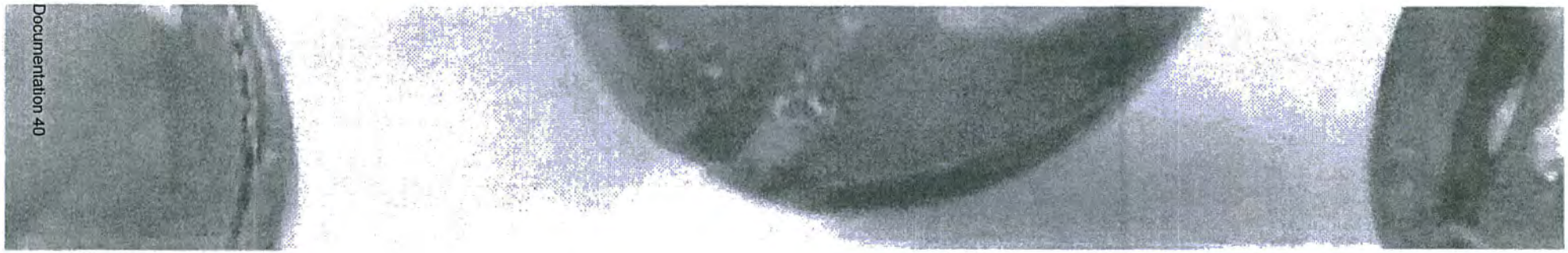

0 IU (placebo) After 3 months


500 IU/day More than 50% reduction


1000 IU/day More than 65% reduction


2000 IU/day More than 80% reduction

Hiremath VP, Rao CB, Naik V, Prasad KVV. Anti-inflammatory Effect of Vitamin D on Gingivitis: A Dose-Response Randomised Control Trial. Oral Health Prev. Dent. 2013; 11(1):61-69. (notes by Seaton)



SENIOR FALLS AND FRACTURES

Vitamin D project helps prevent falls and saves health costs

Published By Live News / August 8, 2013 / No Comments

Source: New Zealand Government – Press Release/Statement:

Headline: Vitamin D project helps prevent falls and saves health costs

Associate Minister of Health Jo Goodhew says MidCentral DHB's vitamin D project is a good example of how a simple intervention can improve lives and save health dollars.

In 2010 the DHB, in partnership with ACC, began encouraging health professionals to prescribe vitamin D to residents in aged care facilities. Between March 2010 and June 2012 the uptake of vitamin D by aged care residents increased from 15 to 74 per cent.

"Comparisons from before and after the start of the project show a 32 per cent reduction in aged residential care residents going to the emergency department with falls-related fractures, and a 41 per cent reduction in their hospital admissions due to these fractures." Mrs Goodhew said.

"The benefits of preventing falls in older people cannot be overstated. Preventing falls enables older people to maintain their independence and confidence.

"Of older people who suffer a hip fracture, nearly 20 per cent will die within a year. Almost half will require long-term care and half will require help at home. Half of those who walked without help before fracturing a hip will be unable to walk without assistance in the year following the fracture."

The vitamin D project is also estimated to have saved MidCentral DHB more than $540,000 because of fewer people coming to the emergency department and reduced admissions to hospital. Further savings are also likely because of reduced need for clinical support, hospital pharmacy services, and physiotherapy and rehabilitation services.

International evidence shows that taking vitamin D significantly reduces older adults' risk of falling.

"We know older people are less likely to fall and injure themselves if they keep their muscles and bones in good condition.

Vitamin D has been shown to increase the number and size of type II muscle fibres, which play an important role in balance and mobility. Vitamin D also helps maintain bone strength," MidCentral DHB pharmacy advisor Andrew Orange says.

The Health Quality & Safety Commission's national patient safety campaign *Open for better care* is currently focusing on falls prevention. For more information about the *Open* campaign, go to www.open.hqsc.govt.nz.

MAYO CLINIC

Vitamin D for Health: A Global Perspective

Arash Hossein-nezhad, MD, PhD, and Michael F. Holick, PhD, MD

Abstract

It is now generally accepted that vitamin D deficiency is a worldwide health problem that affects not only musculoskeletal health but also a wide range of acute and chronic diseases. However, there remains cynicism about the lack of randomized controlled trials to support the association studies regarding the nonskeletal health benefits of vitamin D. This review was obtained by searching English-language studies published up to April 1, 2013, in PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials (search terms: *vitamin D* and *supplementation*) and focuses on recent challenges regarding the definition of vitamin D deficiency and how to achieve optimal serum 25-hydroxyvitamin D concentrations from dietary sources, supplements, and sun exposure. The effect of vitamin D on fetal programming epigenetics and gene regulation could potentially explain why vitamin D has been reported to have such wide-ranging health benefits throughout life. There is potentially a great upside to increasing the vitamin D status of children and adults worldwide for improving musculoskeletal health and reducing the risk of chronic illnesses, including some cancers, autoimmune diseases, infectious diseases, type 2 diabetes mellitus, neurocognitive disorders, and mortality.

 ■ Mayo Clin Proc. 2013;88(7):720-755

From the Department of Medicine, Section of Endocrinology, Nutrition, and Diabetes, Vitamin D, Skin, and Bone Research Laboratory, Boston University Medical Center, Boston, MA.

Vitamin D deficiency has been recognized as a pandemic with a myriad of health consequences.[1,2] Low vitamin D status has been associated with an increased risk of type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity, allergy, and even frailty.[1-4] Low prenatal and neonatal vitamin D status may also increase susceptibility to schizophrenia, type 1 diabetes, and multiple sclerosis (MS) in later life via specific target organ effects, including the immune system, or through epigenetic modification.[5]

Despite the many important health benefits of vitamin D, there is controversy regarding the definition of vitamin D deficiency and what the vitamin D requirement should be.[2,6,7] In addition, critical windows of exposure to adequate vitamin D levels during fetal maturation remain to be defined[5,6] owing, in part, to the lack of well-designed controlled clinical trials with long-term follow-up.[5-7]

This review, obtained, in part, from searching English-language studies published up to April 1, 2013, in PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials (search terms: *vitamin D* and *supplementation*), focuses on recent challenges about how to achieve an optimal serum level of 25-hydroxyvitamin D [25(OH)D] from dietary sources, supplements, and sun exposure and evidence-based benefits for skeletal and nonskeletal health. Also, we explore fetal programming and epigenomic mechanisms that could potentially explain why vitamin D has been reported to have such wide-ranging health benefits throughout life.

VITAMIN D METABOLISM AND BIOLOGICAL FUNCTIONS

Vitamin D (D represents D_2, D_3, or both) is a secosterol produced endogenously in the skin from sun exposure or obtained from foods that naturally contain vitamin D, including cod liver oil and fatty fish (eg, salmon, mackerel, and tuna); UV-irradiated mushrooms; foods fortified with vitamin D; and supplements.[2,7]

During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D_3. The 7-DHC is present in all the layers of human skin.[7-9] Approximately 65% of 7-DHC is found in the epidermis, and greater than 95% of the previtamin D_3 that is produced is in the viable epidermis and, therefore, cannot be removed from the skin when it is washed.[9] Once previtamin D_3 is synthesized in the skin, it can undergo either a photoconversion to lumisterol, tachysterol, and 7-DHC or a heat-induced membrane-enhanced isomerization to vitamin D_3 (Figure 1).[7,8] The cutaneous production of previtamin D_3 is regulated. Solar photoproducts (tachysterol and

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lumisterol) inactive on calcium metabolism are produced at times of prolonged exposure to solar UV-B radiation, thus preventing sun-induced vitamin D intoxication.[7,8] Vitamin D_3 is also sensitive to solar irradiation and is, thereby, inactivated to suprasterol 1 and 2 and to 5,6-trans-vitamin D_3.[7] Cutaneous vitamin D_3 production is influenced by skin pigmentation, sunscreen use, time of day, season, latitude, altitude, and air pollution.[1,2,7,8] An increase in the zenith angle of the sun during winter and early morning and late afternoon results in a longer path for the solar UV-B photons to travel through the ozone layer, which efficiently absorbs them. This is the explanation for why above and below approximately 33° latitude little if any vitamin D_3 is made in the skin during winter.[10,11] This is also the explanation for why—whether being at the equator and in the far northern and southern regions of the world in summer, where the sun shines almost 24 hours a day—vitamin D_3 synthesis occurs only between approximately 10 AM and 3 PM.[1,11] Similarly, in urban areas, such as Los Angeles, California, and Mexico City, Mexico, where nitrogen dioxide and ozone levels are high, few vitamin D_3–producing UV-B photons reach the people living in these cities.[7,11] Similarly, because glass absorbs all UV-B radiation, no vitamin D_3 is produced in the skin when the skin is exposed to sunlight that passes through glass.

Once formed, vitamin D_3 is ejected out of the keratinocyte plasma membrane and is drawn into the dermal capillary bed by the vitamin D binding protein (DBP).[7,8] Vitamin D that is ingested is incorporated into chylomicrons, which are released into the lymphatic system, and enters the venous blood,[2,7] where it binds to DBP and lipoproteins transported to the liver.[1,2,7] Vitamin D_2 and vitamin D_3 are 25-hydroxylated by the liver vitamin D-25-hydroxylase (CYP2R1) to produce the major circulating vitamin D metabolite, 25(OH)D, which is used to determine a patient's vitamin D status.[1,2,7] This metabolite undergoes further hydroxylation by the 25(OH)D-1α-hydroxylase (CYP27B1) in the kidneys to form the secosteroid hormone 1α,25-dihydroxyvitamin D [1,25$(OH)_2$D] (Figure1).[2,7,12] The 25(OH)D bound to DBP is filtered in the kidneys and is reabsorbed in the proximal renal tubules by megalin cubilin receptors.[6,12] The renal 1α-hydroxylation is closely regulated, being enhanced by parathyroid hormone (PTH), hypocalcemia, and hypophosphatemia and inhibited by hyperphosphatemia, fibroblast growth factor-23, and 1,25$(OH)_2$D itself.[7,13,14]

The 1,25$(OH)_2$D performs many of its biologic functions by regulating gene transcription through a nuclear high-affinity vitamin D receptor (VDR).[15,16] This active metabolite of vitamin D binds to the nuclear VDR, which binds retinoic acid X receptor to form a heterodimeric complex that binds to specific nucleotide sequences in the DNA known as vitamin D response elements. Once bound, a variety of transcription factors attach to this complex, resulting in either up-regulation or down-regulation of the gene's activity.[2,7,17] There are estimated to be 200 to 2000 genes that have vitamin D response elements or that are influenced indirectly, possibly by epigenetics, to control a multitude of genes across the genome.[2,16] A recent microarray study on the influence of vitamin D status and vitamin D_3 supplementation on genome-wide expression in white blood cells before and after vitamin D_3 supplementation found that an improved serum 25(OH)D concentration was associated with at least a 1.5-fold alteration in the expression of 291 genes.[17] This study suggested that any improvement in vitamin D status will significantly affect the expression of genes that have a variety of biologic functions of

ARTICLE HIGHLIGHTS

- Vitamin D deficiency is a common underdiagnosed condition.
- Recent evidence from hundreds of studies suggests that vitamin D is important for reducing the risk of type I diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity, allergy, and even frailty.
- The blood level of 25(OH)D is the best method to determine vitamin D status.
- Vitamin D deficiency during pregnancy may influence fetal "imprinting" that may affect chronic disease susceptibility soon after birth as well as later in life.
- An effective strategy to prevent vitamin D deficiency and insufficiency is to obtain some sensible sun exposure, ingest foods that contain vitamin D, and take a vitamin D supplement.

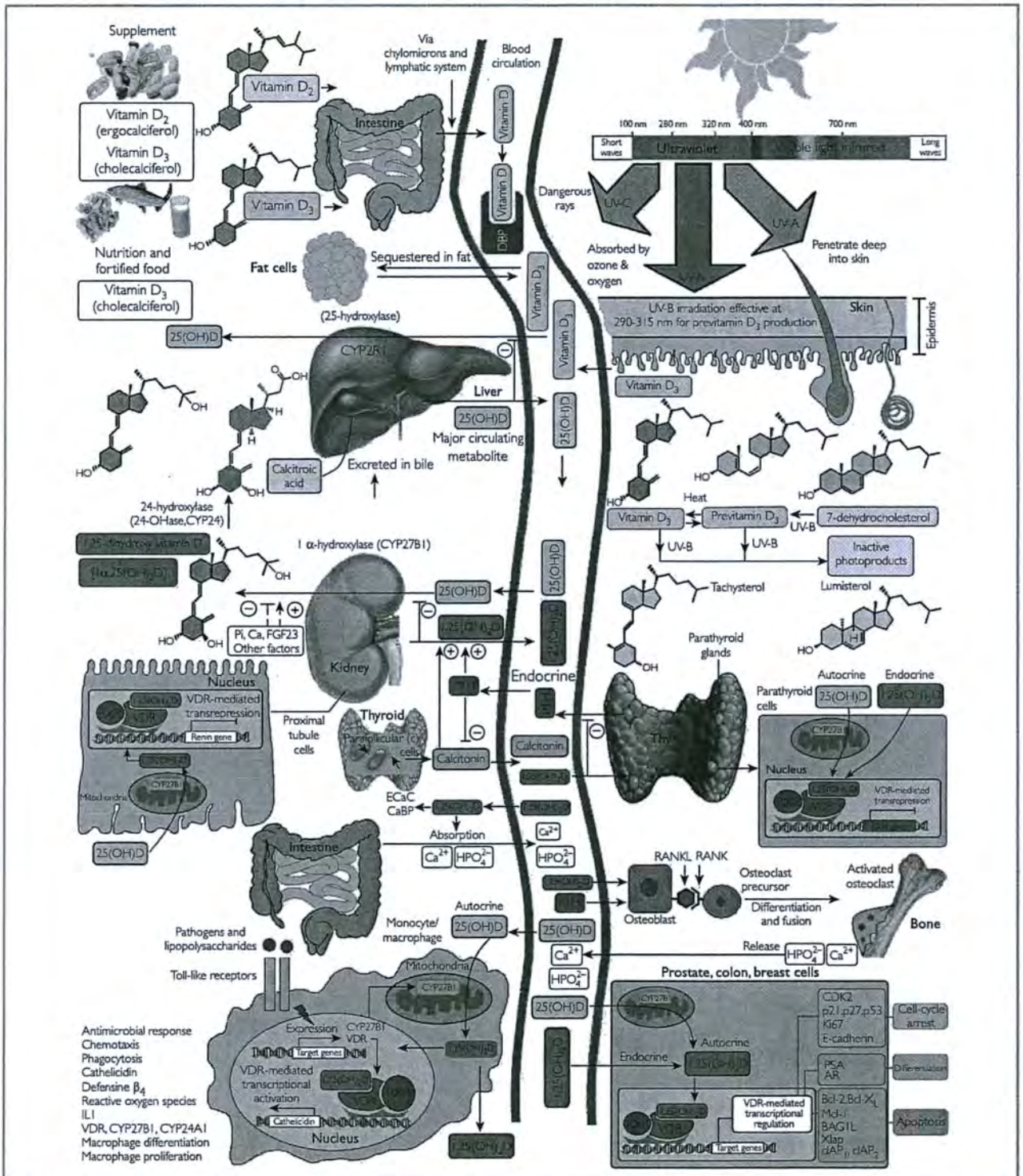

FIGURE 1. Schematic representation of the synthesis and metabolism of vitamin D for skeletal and nonskeletal function. 1-OHase = 25-hydroxyvitamin D-1α-hydroxylase; 24-OHase = 25-hydroxyvitamin D-24-hydroxylase; 25(OH)D = 25-hydroxyvitamin D; $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; CaBP = calcium-binding protein; CYP27B1, Cytochrome P450-27B1; DBP = vitamin D–binding protein; ECaC = epithelial calcium channel; FGF-23 = fibroblast growth factor-23; PTH = parathyroid hormone; RANK = receptor activator of the NF-kB; RANKL = receptor activator of the NF-kB ligand; RXR = retinoic acid receptor; TLR2/1 = Toll-like receptor 2/1; VDR = vitamin D receptor; vitamin D = vitamin D_2 or vitamin D_3. Copyright Holick 2013, reproduced with permission.

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more than 80 pathways linked to cancer, autoimmune disorders, and cardiovascular disease, which have been associated with vitamin D deficiency.[17]

One of the major physiologic functions of vitamin D is to maintain serum calcium and phosphorus levels in a healthy physiologic range to maintain a variety of metabolic functions, transcription regulation, and bone metabolism (Figure 1).[2,7] The $1,25(OH)_2D$ interacts with its VDR in the small intestine to increase the efficiency of intestinal calcium absorption from approximately 10% to 15% up to 30% to 40% and intestinal phosphorus absorption from approximately 60% to 80%.[7] It also interacts with VDR in osteoblasts to stimulate a receptor activator of nuclear factor κB ligand, which, in turn, interacts with receptor activator of nuclear factor κB on immature preosteoclasts, stimulating them to become mature bone-resorbing osteoclasts (Figure 1).[7,18] The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. In the kidneys, $1,25(OH)_2D$ stimulates calcium reabsorption from the glomerular filtrate.[2,7]

The VDR is present in most tissues and cells in the body.[1,2,7,19-25] Many of these organs and cells, including the brain, vascular smooth muscle, prostate, breast, and macrophages, not only have a VDR but also have the capacity to produce $1,25(OH)_2D$.[1,2,7,19-25] This production probably depends on the availability of circulating 25(OH)D, indicating the biological importance of sufficient blood levels of this vitamin D metabolite.[2,15,26]

The estimated 2000 genes that are directly or indirectly regulated by $1,25(OH)_2D$[2,7,17-24,26] have a wide range of proven biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inducing apoptosis, inhibiting renin production, and stimulating macrophage cathelicidin production.[1,2,7,16,17,26] In addition, $1,25(OH)_2D$ stimulates its own destruction in the kidneys and in cells that have a VDR and responds to $1,25(OH)_2D$ by enhancing expression of the 25(OH)D–24-hydroxylase (CYP24A1) to metabolize 25(OH)D and $1,25(OH)_2D$ into water-soluble inactive forms that are excreted in the bile (Figure 1).[1,7,19,27]

VITAMIN D METABOLISM DURING PREGNANCY

Vitamin D metabolism is enhanced during pregnancy and lactation. The placenta is formed at 4 weeks of gestation.[2,25] From this time to term, 25(OH)D is transferred across the placenta, and the fetal cord blood concentration of 25(OH)D is correlated with the mother's concentration.[27] However, the active metabolite $1,25(OH)_2D$ does not readily cross the placenta.[25,27] The fetal kidneys and the placenta provide the fetal circulation with $1,25(OH)_2D$ by expressing CYP27B1 (Figure 2).[28]

The maternal (decidual) and fetal placental (trophoblastic) components of the placenta have CYP27B1 activity; cultured human syncytiotrophoblasts and decidual cells synthesize $1,25(OH)_2D_3$.[27] The spatiotemporal organization of placental CYP27B1 and the VDR across gestation has also been characterized, confirming that the enzyme and receptor are localized to the maternal and fetal parts of the placenta.[29] Serum levels of DBP increase 46% to 103% during pregnancy, suggesting that DBP may play a role in directing vitamin D metabolism and function during pregnancy.[2,27,30] The DBP has a much higher binding affinity for 25(OH)D than for $1,25(OH)_2D$, and in kidney epithelial cells, DBP plays a pivotal role in conserving 25(OH)D by facilitating the recovery of 25(OH)D from the glomerular filtrate.[31,32]

Transplacental transfer of calcium to the fetus is also facilitated by expression of all the key mediators of vitamin D metabolism in the placenta. Hormones involved in fetal growth and that influence CYP27B1 activity include insulin-like growth factor 1 and human placental lactogen, PTH-related protein (PTHrP), estradiol, and prolactin.[2,31,33,34] The PTHrP acts as a calciotropic hormone during fetal life and in lactation.[35-37] The exact role of circulating PTHrP in pregnancy is unknown, but its rise may stimulate renal CYP27B1 and contribute to the increase in $1,25(OH)_2D$ concentration and, indirectly, the suppression of PTH levels.[27,35,37] The PTHrP arises from several sources, including the breast, myometrium, decidua, amnion, and fetal parathyroids.[36] Several roles of PTHrP are postulated from animal studies, including fetal chondrocyte maturation, fetal calcium transfer, and stimulation of CYP27B1 activity.[33,34,36] Furthermore, the carboxy terminal of PTHrP (osteostatin) may suppress osteoclastic activity

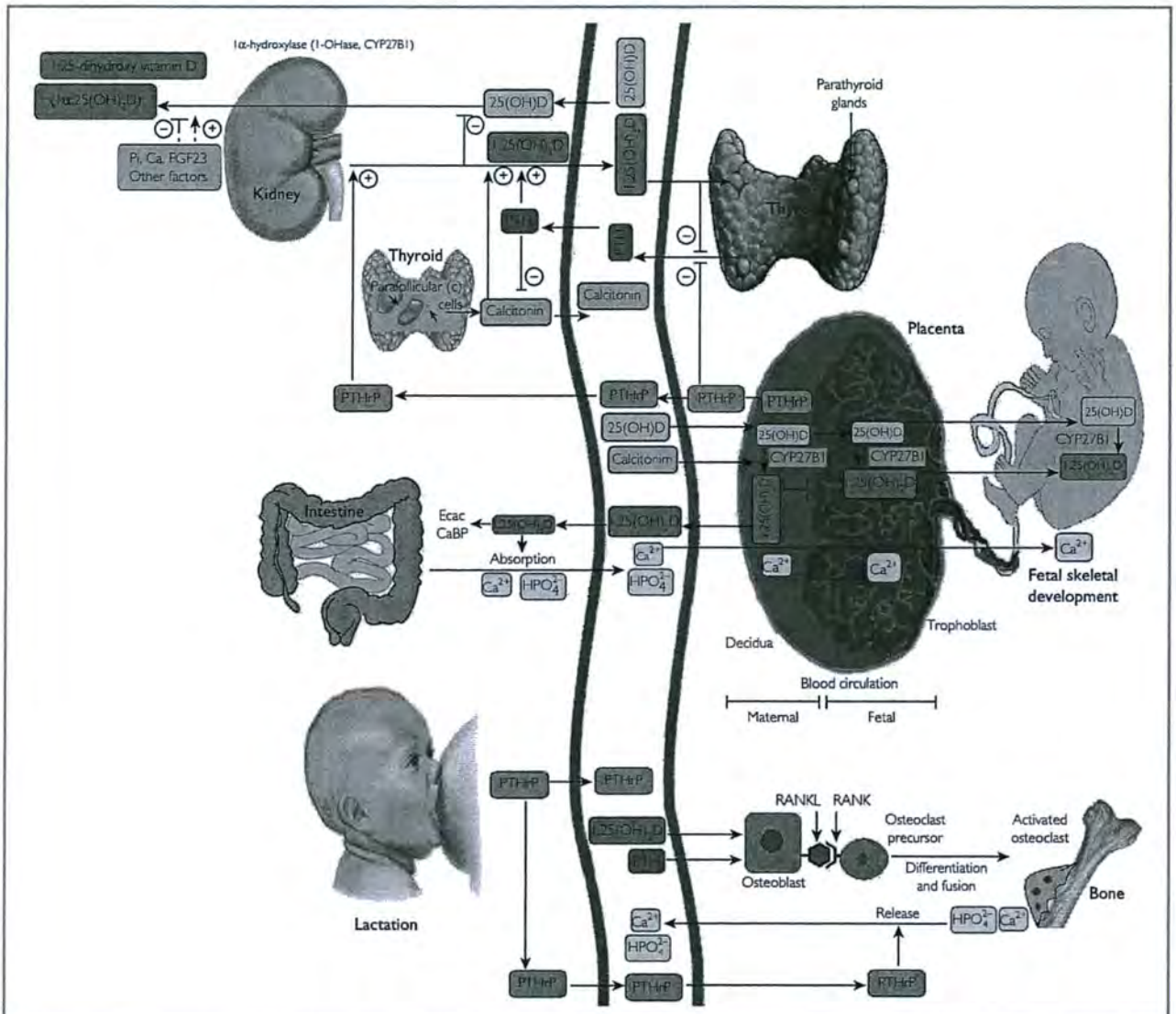

FIGURE 2. Vitamin D metabolism during pregnancy and lactation. Maternal 25(OH)D is thought to freely cross the human placenta. The placenta expresses vitamin D receptors (VDR) and also produces 1-OHase to convert 25(OH)D to $1,25(OH)_2D$. 1,25-dihydroxyvitamin D does not readily cross the placenta, and fetal $1,25(OH)_2D$ levels are normally lower than maternal serum levels. The low fetal concentrations of $1,25(OH)_2D$ reflect the low fetal PTH and high phosphorus concentrations, which suppress renal 1-OHase. Although PTHrP is elevated in the fetal circulation, it appears to be less able to stimulate the renal 1-OHase than PTH. Total (free and bound) $1,25(OH)_2D$ concentrations double or triple in the maternal circulation starting in the first trimester, but studies have only shown increased free concentrations during the third trimester. This increase is due to maternal synthesis by the renal 1-OHase. Vitamin D passes readily into breast milk. 25(OH)D passes very poorly, and $1,25(OH)_2D$ does not appear to pass at all.[2] $1,25(OH)_2D$ levels fall rapidly after pregnancy and are normal during lactation.[7] Near-exclusive breastfeeding for 6 months leads, on average, to maternal calcium loss 4 times higher than that in pregnancy. Phosphorus can rise above the normal range, probably because of accelerated resorption from the skeleton. Parathyroid hormone-related protein levels are higher than PTH concentrations in nonpregnant women and show some pulsatility in response to suckling. Parathyroid hormone-related protein (produced by the lactating breast) in combination with low estradiol concentrations appears to drive the main physiologic adaptation to meet the calcium demands of lactation. Suckling and prolactin both inhibit ovarian function and stimulate PTHrP. Together, PTHrP and low estradiol concentrations stimulate skeletal resorption. Renal calcium reabsorption rates increase, presumably due to PTHrP, which mimics the actions of PTH on the renal tubules. *For definitions of abbreviations, see Figure 1.* Copyright Holick 2013, reproduced with permission.

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and may have a possible bone protection role in the mother during pregnancy.[32,35-37]

Calcitonin, an important component of calcium homeostasis during pregnancy,[38,39] is known to promote transcription of CYP27B1[40] and may, therefore, be a key determinant of placental vitamin D metabolism.[41] Thus, PTHrP and calcitonin, as well as other factors, cause $1,25(OH)_2D$ levels to increase, being 2-fold higher in serum of women in the third trimester of pregnancy than in nonpregnant or postpartum women.[2,27] Normally, $1,25(OH)_2D$ regulates its own metabolism via a feedback loop such that elevated concentrations induce the expression of CYP24A1, with concomitant down-regulation of CYP27B1.[7,25,42] This process results in a reduction of 25(OH)D and $1,25(OH)_2D$ levels.[9,29,30] However, during pregnancy, this process becomes uncoupled, resulting in elevated maternal concentrations of circulating $1,25(OH)_2D$.[27,43] The placental methylation of the CYP24A1 promoter reduces the capacity for CYP24A1 induction and down-regulates basal promoter activity and abolishes vitamin D–mediated feedback activation. This epigenetic decoupling of vitamin D feedback catabolism also plays an important role in enhancing $1,25(OH)_2D$ bioavailability at the fetomaternal interface.[44]

VITAMIN D, PLACENTA DEVELOPMENT, FETAL PROGRAMMING, AND EPIGENETIC MODIFICATION

Epidemiologic evidence has suggested a link between fetal life events and susceptibility to disease in adult life.[45-47] This paradigm, referred to as *fetal programming* or *developmental origins of health and disease,* may have a profound effect on public health strategies for the prevention of major illnesses.[2,48] The role of vitamin D in implantation tolerance and placental development has been studied. The $1,25(OH)_2D_3$ regulates key target genes associated with implantation, such as Homeobox A10 (*HOXA10*), whereas the potent immunosuppressive effects of $1,25(OH)_2D_3$ suggest a role in placental development.[49] Increasing expression of CYP27B1 and VDR in first-trimester human trophoblasts and deciduas[50] may be related to the immunosuppressive effects of $1,25(OH)_2D_3$ and may help improve implantation tolerance. Placental development plays a critical role in pregnancy health, and its link to maternal vitamin D deficiency may explain related adverse outcomes.[5,45] In neonatal rats exposed prenatally to low maternal serum 25(OH)D levels, there was a general slowing of cardiac development, with significantly lower heart weights, decreased citrate synthase and 3-hydroxyacyl CoA dehydrogenase activity, and a 15% lower myofibrillar protein content.[46] A 2-month-old human infant with dilated cardiomyopathy and severe vitamin D deficiency had dramatic improvement of her ejection fraction (17%-66%) after vitamin D supplementation.[47] In addition, maternal vitamin D deficiency in rats stimulated nephrogenesis in offspring, with a 20% increase in nephron number but a decrease in renal corpuscle size observed between replete and deficient rats, despite there being no difference in body weight or kidney weight and volume.[5,51] These findings support the role of vitamin D influencing fetal programming and placental development.

Epigenetic modification refers to heritable changes in gene expression that are not mediated by alterations in DNA sequence.[52] This hypothesis, first articulated by Barker et al,[53] postulated that in utero epigenetic fetal programming (as a result of environmental events during pregnancy) induced specific genes and genomic pathways that controlled fetal development and subsequent disease risk. The role of vitamin D in epigenetic modification and fetal programming could potentially explain why vitamin D has been reported to have such wide-ranging health benefits. Recent studies have suggested that epigenetic decoupling of vitamin D feedback catabolism plays an important role in maximizing $1,25(OH)_2D$ bioavailability at the fetomaternal interface.[25,44] Modified expression of the genes encoding placental calcium transporters, by epigenetic regulation by $1,25(OH)_2D$, might represent the means whereby maternal vitamin D status could influence bone mineral accrual in the neonate.[54,55] Vitamin D deficiency during pregnancy may, therefore, not only impair maternal skeletal preservation and fetal skeletal formation but also influence fetal "imprinting" that may affect chronic disease susceptibility soon after birth as well as later in life (Figure 3).[15,56] Transgenerational hormonal imprinting caused by vitamin D treatment of newborn rats has been previously reported.[57] A recent study reported that VDR binds to the ε germline gene promoter and exhibits transrepressive activity.[58] Inhibition

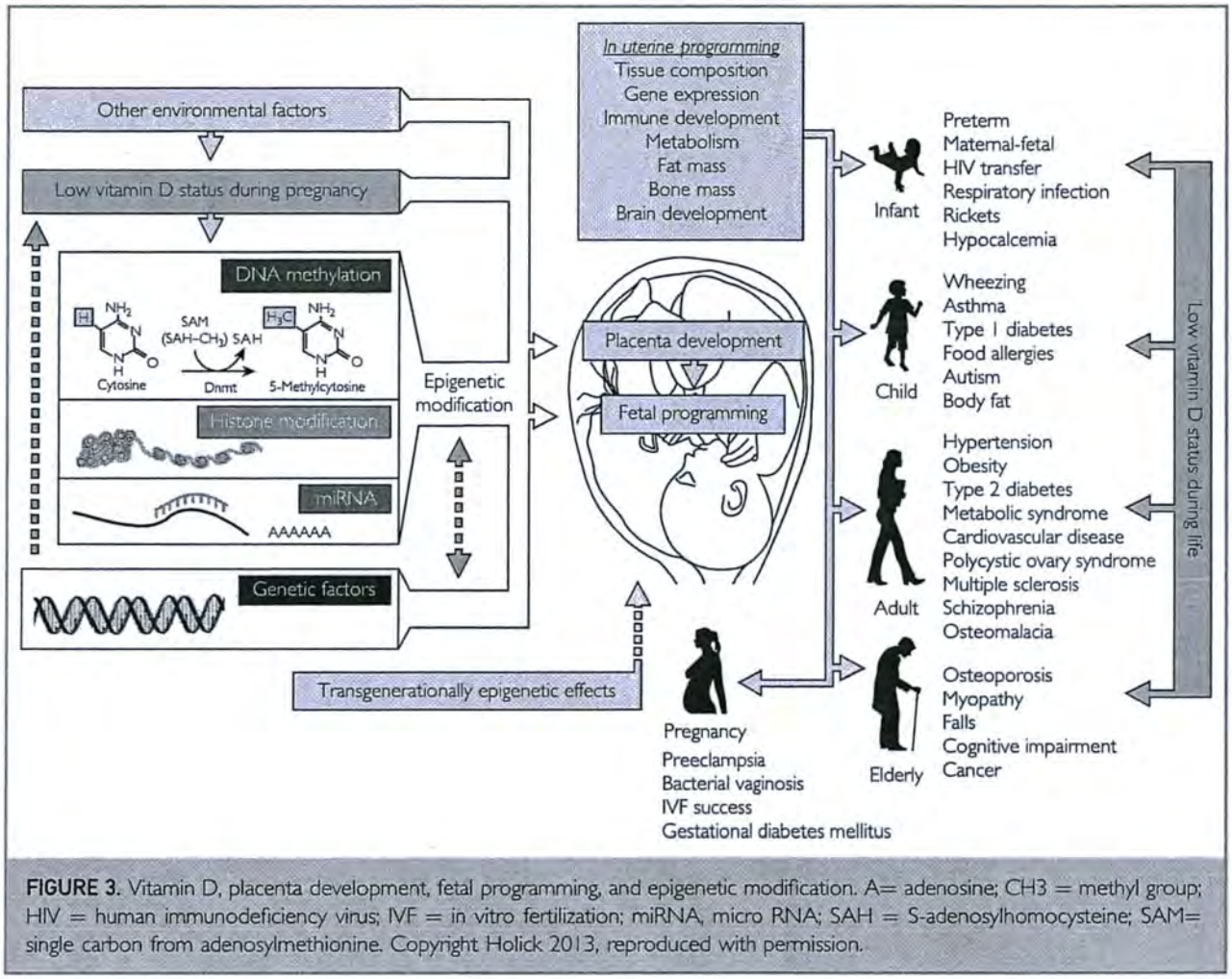

FIGURE 3. Vitamin D, placenta development, fetal programming, and epigenetic modification. A= adenosine; CH3 = methyl group; HIV = human immunodeficiency virus; IVF = in vitro fertilization; miRNA, micro RNA; SAH = S-adenosylhomocysteine; SAM= single carbon from adenosylmethionine. Copyright Holick 2013, reproduced with permission.

of IgE production by $1,25(OH)_2D$ was mediated by its transrepressive activity through the VDR-corepressor complex, affecting chromatin compacting around the Iε region.[58] Also, the associations of early-life sun exposure and germline variation in VDR and CYP24A1 with non-Hodgkin lymphoma risk was reported in a clinic-based case-control study.[59]

DEFINITION OF VITAMIN D DEFICIENCY

The blood level of 25(OH)D is the best method to determine vitamin D status. Although $1,25(OH)_2D$ is the biologically active form, it provides no information about vitamin D status because it is often normal or even elevated in children and adults who are vitamin D deficient.[7,15,60-63] Recently, the Institute of Medicine (IOM) and the Endocrine Society released separate guidelines for vitamin D requirements.[60,62] The recommended dietary allowances (RDAs) of the IOM and the Endocrine Society guidelines for vitamin D intake are summarized in Figure 4.

The revised guidelines by the IOM stress that the daily requirements for vitamin D are generally met by most of the population and are appropriate to reach the "sufficient" level of 20 ng/mL (to convert to nmol/L, multiply by 2.496).[62] The IOM guidelines used a population model to prevent vitamin D deficiency in 97.5% of the general population. Also, note that the IOM report focuses only on bone health (calcium absorption, bone mineral density, and osteomalacia/rickets) and found no evidence that a serum 25(OH)D concentration greater than 20 ng/mL had beneficial effects at a population level. However, considering the available evidence on skeletal and extraskeletal effects of vitamin D, the few negative studies, and the lack of toxicity potential of vitamin D supplementation at

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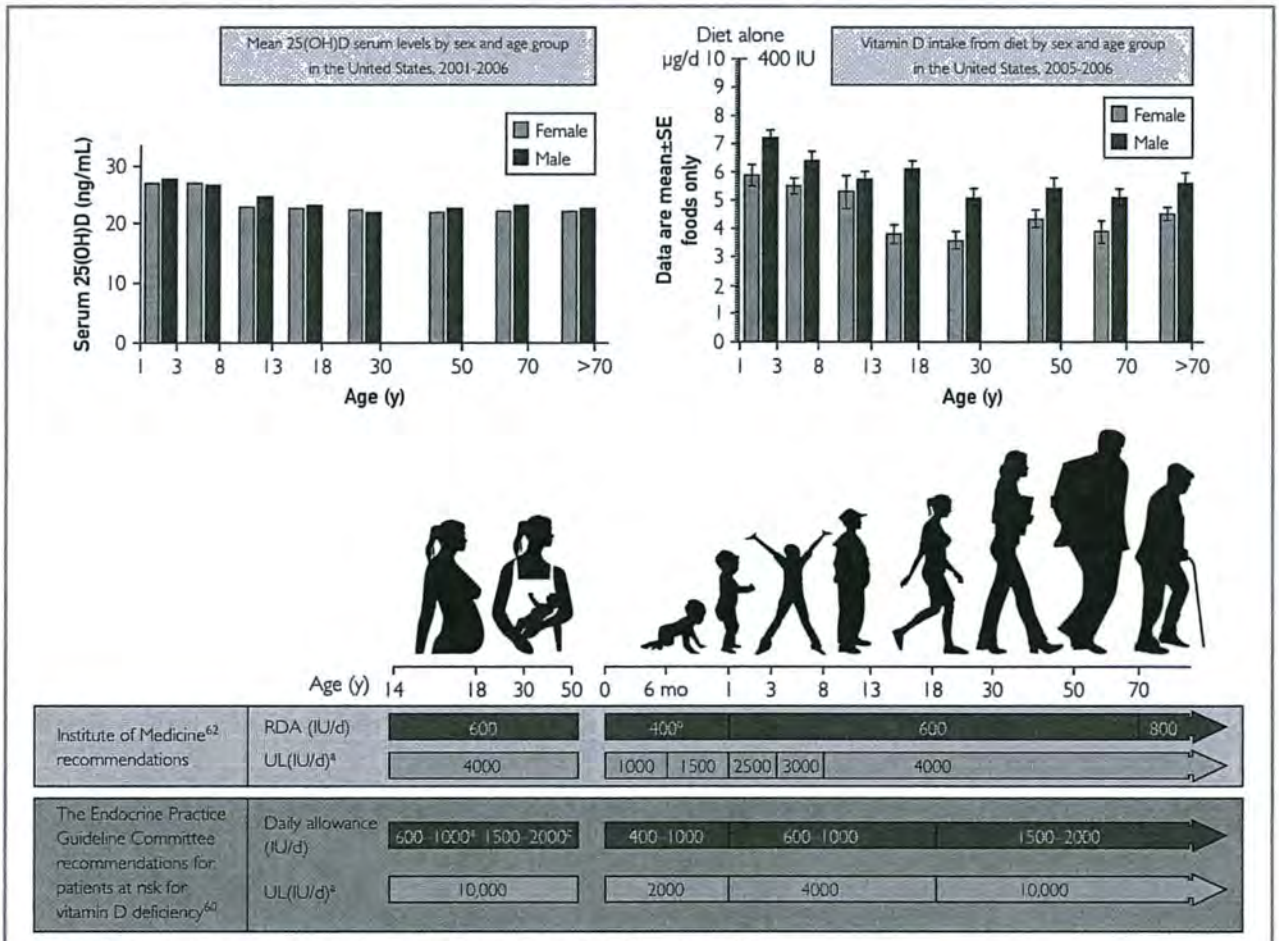

[a] UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake.
[b] Reflects AI reference value rather than RDA. RDAs have not been established for infants.
[c] Mother's requirement 4000-6000 (mother's intake for infant's requirement if infant is not receiving 400 IU/d).

FIGURE 4. Vitamin D intakes recommended by the Institute of Medicine and the Endocrine Practice Guidelines Committee. 25(OH)D = 25-hydroxyvitamin D; AI= adequate intake; RDA = recommended dietary allowance; SE = standard error; UL= tolerable upper intake level. Copyright Holick 2013, reproduced with permission.

recommended doses, the US Endocrine Society, which used a medical model, recommended that serum 25(OH)D levels of 30 ng/mL should be attained to avoid other risks connected with an inadequate vitamin D status.[7,60] Therefore, the Endocrine Society recommended that vitamin D deficiency be defined as a 25(OH)D level of 20 ng/mL or less, vitamin D insufficiency as 21 to 29 ng/mL, and vitamin D sufficiency as 30 ng/mL or greater for children and adults.[60] It suggested that maintenance of a 25(OH)D level of 40 to 60 ng/mL is ideal (this takes into account assay variability) and that up to 100 ng/mL is safe.[60]

MUSCULOSKELETAL CONSEQUENCES OF VITAMIN D DEFICIENCY

According to current evidence from biochemical testing, observational studies, and randomized controlled trials (RCTs), serum 25(OH)D levels of at least 20 ng/mL are required for normalization of PTH levels, to minimize the risk of osteomalacia, and for optimal bone and muscle function, with many experts regarding 30 ng/mL as the threshold for optimal bone health.[7,16,61,64-66] The skeletal consequences of 25(OH)D insufficiency include secondary hyperparathyroidism, increased bone turnover and bone loss, and increased risk of low-trauma fractures.[7,15,61,64]

The most common etiology of rickets, historically and presently, is vitamin D deficiency. Low maternal 25(OH)D levels were found to correlate with increased fetal distal femoral splaying, determined by ultrasonography measurements of femoral length and metaphyseal width.[63,65] Children begin to manifest classic clinical signs of rickets between 6 months and 1.5 years that include rachitic rosary, widened epiphyseal plates at the end of long bones, and bowing deformities of the legs.[66] A common early symptom in newborns is excessive sweating due to neuromuscular irritability,[66] and a 25(OH)D level less than 20 ng/mL is common in children presenting with vague limb or back pain.

From a skeletal perspective for adults, evidence from RCTs suggests that vitamin D may be considered a threshold nutrient, with little bone benefit observed at levels of 25(OH)D above which PTH is normalized.[62,67] A literature review of 70 studies generally found a threshold for a decline in serum PTH levels with increasing serum 25(OH)D levels, but there was no consistency in the threshold level of serum 25(OH)D, which varied from 20 to 50 ng/mL.[68] A study of 4100 older adults (>60 years old) from the Third National Health and Nutrition Examination Survey (NHANES III) found that higher 25(OH)D levels were associated with better lower extremity function.[61] Much of the improvement occurred at 25(OH)D levels ranging from 9 to 16 ng/mL but continued to be seen at levels up to 40 ng/mL.[69] A systematic review revealed that supplemental vitamin D at daily doses of 800 to 1000 IU consistently had beneficial effects on muscle strength and balance.[70] Several RCTs have reported positive effects of vitamin D supplementation on muscle function and fall prevention.[71-73] Adequate calcium intake is imperative to gain optimal benefit from improving the vitamin D status in those with insufficient 25(OH)D levels.[67] In contrast, a study of 173 young Asian Indian females revealed that after supplementation with vitamin D_3 (60,000 IU/wk for 8 weeks followed by 60,000 IU every 2 weeks) and calcium (500 mg twice per day for 6 months), and despite significant improvement in serum 25(OH)D levels, there was no significant change in their skeletal muscle strength.[74] Thus, age, baseline and final 25(OH)D concentrations, and whether and how much calcium supplementation was included in the clinical trial could affect outcome measures related to muscle performance and vitamin D status.

Proximal muscle weakness is a prominent clinical feature of vitamin D deficiency.[7,60] The relative contributions of vitamin D and calcium for reducing fracture risk remain unclear[75] because improving calcium intake is also associated with suppression of PTH levels independent of vitamin D status.[67,76,77] A meta-analysis of data from RCTs found a dose-response relationship between a higher vitamin D dose and higher achieved serum 25(OH)D levels, with prevention of falls and fractures.[73] The greatest benefit was observed at 700 to 1000 IU/d or a mean serum 25(OH)D concentration of 30 to 44 ng/mL.[71,73] Similar results were reported in a more recent meta-analysis of pooled participant-level data from 11 double-blind RCTs of oral vitamin D supplementation, with or without calcium, compared with placebo or calcium alone in persons 65 years or older.[78] Reduction in the risk of fracture occurred only at the highest vitamin D intake level (median, 800 IU/d; range, 792-2000 IU/d), with a 30% reduction in the risk of hip fracture and a 14% reduction in the risk of any nonvertebral fracture.[78] This reduction was independent of the assigned treatment dose of vitamin D, age group, sex, type of dwelling, and study.[78] Several previous meta-analyses have suggested that the dose of vitamin D is irrelevant when vitamin D is combined with calcium.[79-82] In contrast, a pooled subgroup analysis of the 8 double-blind RCTs that used vitamin D combined with calcium indicated that with combined supplementation, the risk of fracture was reduced only at the highest actual intake level of vitamin D. These findings support that a 25(OH)D level of more than 24 ng/mL may be most beneficial for reducing the risk of fractures.[78]

With a similar tone and theme, a report from the US Preventive Services Task Force concluded that current evidence is insufficient to assess the balance of benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men.[83] Furthermore, they concluded that there was insufficient evidence to assess the balance of benefits and harms of daily supplementation with greater than 400 IU of vitamin D_3 and greater than 1000 mg of calcium for primary prevention of fractures in noninstitutionalized postmenopausal women.

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They recommended against daily supplementation with 400 IU or less of vitamin D_3 and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women. They also stated that it was unclear whether higher doses of vitamin D and calcium are effective in preventing fractures in postmenopausal women, younger women, or men.[83] The Task Force, however, concluded that vitamin D supplementation is effective in preventing falls in community-dwelling adults 65 years or older, which, in turn, reduces the risk of fracture. This could help explain the observation by the Women's Health Initiative (WHI) that, in the subgroup of long-adherent women who took their calcium and vitamin D, there was a reduced risk of hip but not total fractures.[84] Therefore, what is still unknown is whether adequate intake of calcium, especially from dietary sources, and maintenance of serum 25(OH)D levels of at least 20 ng/mL as recommended by the IOM[62] or at least 30 ng/mL as recommended by the Endocrine Society[60] throughout life will reduce the risk of fracture. Most evidence suggests that adequate calcium and vitamin D intake along with exercise during childhood will maximize bone mineral content that can be sustained in young and middle-aged adults as long as they also have a healthy lifestyle, adequate calcium intake, and a healthy vitamin D status.[60-62,84-86] Accruing maximum bone mineral content during childhood, and maintaining peak bone mineral density in young and middle-aged adults, will likely reduce the risk of fracture later in life, when there is a disruption in bone remodeling due to menopause and aging.

Recent recommendations of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO)[87] for the optimal management of elderly and postmenopausal women regarding vitamin D supplementation have also indicated that patients with serum 25(OH)D levels less than 20 ng/mL have increased bone turnover, bone loss, and, possibly, mineralization defects compared with patients with serum 25(OH)D levels of 20 ng/mL or greater. Similar relationships have been reported for frailty, nonvertebral and hip fracture, and all-cause mortality, with poorer outcomes at less than 20 ng/mL.[87] Thus, ESCEO recommended that 20 ng/mL be the minimal serum 25(OH)D concentration at the population level and in patients with osteoporosis to ensure optimal bone health. Also, in fragile elderly individuals who are at elevated risk for falls and fractures, ESCEO recommended a minimal serum 25(OH)D level of 30 ng/mL for the greatest effect on fracture.[87] This coincides with the recommendation from the Endocrine Society[60] and with the observation of Priemel et al,[79] who reported that of 675 presumed healthy adults (aged 20-90+ years) who died in an accident, 36% had evidence of osteomalacia. However, Priemel et al[79] observed no osteomalacia in those who had a 25(OH)D level greater than 30 ng/mL.

EVIDENCE-BASED SKELETAL AND NONSKELETAL HEALTH BENEFITS OF VITAMIN D

Observational studies have found a decreased risk of many disorders, including certain types of cancer, mental disorders, infectious disease, cardiovascular disease, type 2 diabetes mellitus, and autoimmune disorders, associated with serum 25(OH)D levels greater than 28 to 32 ng/mL.[7,60,67] It has, therefore, been argued that 25(OH)D levels should be in the range of 28 to 40 ng/mL to maximize these nonskeletal benefits.[1,2,7,19,60,61]

The results of some clinical trials provide evidence confirming the results of observational and association studies, whereas others do not. The Table summarizes the meta-analyses on vitamin D supplementation, comparing the beneficial and nonbeneficial effects of vitamin D supplementation in randomized trials for musculoskeletal and nonskeletal outcomes. The Table provides the foundation for clinical decision making for recommending vitamin D supplementation and identifies gaps in our knowledge that require additional RCTs to provide insights as to whether vitamin D supplementation has nonskeletal health benefits.

VITAMIN D AND NONSKELETAL HEALTH ASSOCIATIONS AND MECHANISMS

Cancers

Association studies have related higher serum levels of 25(OH)D to reduced incidence of many types of cancers. It has been hypothesized that the local conversion of 25(OH)D to $1,25(OH)_2D$ in healthy cells in the colon, breast, and prostate can help prevent malignancy by

TABLE. Summary of Meta-analyses of Vitamin D Supplementation

Reference, year	Included studies	Sample size (No.)	Participants	Dose/duration	Outcomes	Effects
Thorne-Lyman and Fawzi,[88] 2012	5 randomized trials 2 observational studies	28,943	Pregnant women	Vitamin D_2 and vitamin D_3 Various doses and patterns of intake during pregnancy	Perinatal and infant health	Positive effect on low birth weight No effect on small-for-gestational-age (2 trials) No effect on preterm delivery
De-Regil et al,[89] 2012	6 trials	1023	Women during pregnancy	Vitamin D (1200 IU/d) alone or combined with 375 mg of elemental calcium	Safely improve maternal and neonatal outcomes	No effect on preeclampsia Positive effect on concentrations of 25(OH)D in serum Positive effect on birth weight No effect on adverse effects
Bischoff-Ferrari et al,[78] 2012	11 double-blind RCTs	31,022	Persons aged ≥65 y	Oral vitamin D supplementation with or without calcium	Fracture reduction	No effect on risk of hip fracture until 800 IU/d Positive effect on hip and any nonvertebral fracture by highest intake level according to quartiles
Lai et al,[90] 2010	7 eligible RCTs and 17 identified case-control studies	801	Persons aged 74.8-85 y	Vitamin D_2 and vitamin D_3 (400-1100 IU)	Hip fracture risk	No effect on hip fracture risk
Bergman et al,[80] 2010	8 controlled trials	12,658	Postmenopausal women	Vitamin D_3 supplementation (800 IU/d) with or without calcium	Increasing BMD Preventing fractures	Positive effect on nonvertebral and hip fractures
Bischoff-Ferrari et al,[81] 2009	12 double-blind RCTs	83,165	Older individuals (≥65 y)	>400 IU/d	Preventing nonvertebral and hip fractures	Positive effect on nonvertebral fracture prevention with vitamin D is dose dependent (only high dose)
Avenell et al,[82] 2009	45 trials	83,741	Older people	Vitamin D or related compounds	Preventing fractures	Positive effect by vitamin D with calcium on hip fracture No effect by vitamin D alone on hip fracture
Abrahamsen et al,[75] 2010	7 major randomized trials	68,517	Persons aged 47-107 y	Vitamin D_2 and vitamin D_3 (10 μg/d to 300,000 IU/12 mo)	Antifracture efficacy	Positive effect of vitamin D with calcium on fracture No effect of vitamin D alone
Itzaks,[91] 2007	11 trials	NA	General population	Vitamin D_2 and vitamin D_3 follow-up >1 y	Fracture risk	High-dose vitamin D may be effective in institutionalized persons but probably is not effective in the general population
Jackson et al,[92] 2007	9 studies	2410	Postmenopausal women	Vitamin D_3 (excluding the potential effect of calcium supplementation)	Risk of fall and fracture	Positive effect on risk of fall in patients treated with vitamin D_3
Boonen et al,[93] 2007	10 RCTs	54,592	Postmenopausal women and/or older men (≥50 y)	Oral vitamin D with or without calcium vs placebo/no treatment	Prevention of hip fractures	Positive effect of oral vitamin D on reducing the risk of hip fractures only with calcium supplementation
Avenell et al,[94] 2005	57 trials	82,986	Older people	Vitamin D or an analogue, alone or with calcium, vs placebo	Fracture	Positive effect of vitamin D with calcium supplements on hip and other nonvertebral fractures

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Bischoff-Ferrari et al,[84] 2005	5 RCTs for hip fracture 7 RCTs for nonvertebral fracture risk	19,114	Older people	Oral vitamin D supplementation (cholecalciferol, ergocalciferol) with or without calcium supplementation vs calcium supplementation	Preventing hip and nonvertebral fractures	Positive effect (700-800 IU/d) on hip and any nonvertebral fractures in ambulatory or institutionalized elderly persons No effect (400 IU/d) on fracture prevention
Winzenberg et al,[85] 2011	6 studies	884	Healthy children and adolescents (aged 1 mo to <20 y)	Vitamin D supplementation vs placebo for ≥3 mo	Improving BMD (effects vary with factors such as vitamin D dose and vitamin D status)	No effect on total body BMC or on hip or forearm BMD Positive small effect on lumbar spine BMD Positive effect with low serum vitamin D on total body BMC and lumbar spine bone
Huncharek et al,[86] 2008	21 RCTs	NA	Children	Dietary calcium/dairy supplementation	BMC	Positive effect of dietary calcium/dairy products, with and without vitamin D, on total body and lumbar spine BMC in children (with low baseline intakes)
Bischoff-Ferrari et al,[95] 2009	8 RCTs	2426	Older individuals	Vitamin D_2 and vitamin D_3 (200-1000 IU) with or without calcium	Preventing falls	Positive effect of supplemental vitamin D (700-1000 IU/d) on the risk of falling No effect at a dose <700 IU
Kalyani et al,[96] 2010	10 articles	2932	Older adults (aged ≥60 y)	200-1000 IU/d of vitamin D for 1-36 mo	Fall prevention	Positive effect on fall prevention
Chung et al,[97] 2011	19 RCTs (3 for cancer and 16 for fracture outcomes) 28 observational studies (for cancer outcomes)	NA	Adults	Vitamin D with or without calcium (limited data from RCTs assessed high-dose vitamin D [1000 IU/d])	Benefits and harms of vitamin D with or without calcium supplementation on clinical outcomes of cancer and fractures	Positive effect of high-dose vitamin D on reduced risk of total cancer Positive effect on fracture Negative effect on renal and urinary tract stones
Buttigliero et al,[98] 2011	25 studies (3 randomized trials involving patients with advanced prostate cancer explored the prognostic role of vitamin D supplementation)	1273	Cancer patients	1 trial: doxercalciferol 2 trials: calcitriol Duration: 11.7-18.32 mo	Influence of hypovitaminosis D on prognosis of cancer Improvement outcome of vitamin D supplementation	No effect on survival
Bjelakovic et al,[99] 2011	50 randomized trials	94,148	Adults; Most trials included elderly women (>70 y)	Supplemental vitamin D (vitamin D_3 [cholecalciferol] or vitamin D_2 [ergocalciferol]) or an active form of vitamin D (1α-hydroxyvitamin D [alfacalcidol] or 1,25-dihydroxyvitamin D [calcitriol]) at any dose, duration, and route of administration vs placebo or no intervention	Beneficial and harmful effects of vitamin D for prevention of mortality	Positive effect of vitamin D_3 on mortality Negative effect of vitamin D_3 combined with calcium on nephrolithiasis Negative effect on hypercalcemia

Continued on next page

TABLE. Continued

Reference, year	Included studies	Sample size (No.)	Participants	Dose/duration	Outcomes	Effects
Irlam et al,[100] 2010	16 additional trials (only 1 trial was single supplements of vitamin D)	22,120 participants in the trials	Adults and children with HIV infection	NA	Reducing mortality and morbidity	No effect
Autier et al,[101] 2012	76 trials	6207	White persons aged >50 y	Doses of 5-250 μg/d (median, 20 μg/d)	Circulating 25(OH)D level	Positive effect of vitamin D_3 intake without calcium on serum 25(OH)D concentrations No effect of concomitant use of calcium supplementation and high 25(OH)D concentration at baseline
Bjorkman et al,[102] 2009	52 clinical trials	6290	Chronically immobile patients	Vitamin D supplementation	Responses of parathyroid hormone	Positive effect in chronically immobile patients on 25(OH)D levels but a slight effect on PTH decrease
Tripkovic et al,[103] 2012	17 studies	1016	Persons aged 18-97 y	Varying dosages and treatment periods	Compared the effects of vitamin D_2 and vitamin D_3 on serum 25(OH)D concentrations	Positive effect of vitamin D_3 compared with vitamin D_2 in the raising of serum 25(OH)D concentrations
Kandula et al,[104] 2011	22 studies	264	Patients with non–dialysis-dependent CKD, dialysis-dependent CKD, and renal transplant	Ergocalciferol or cholecalciferol	Benefits and harms of vitamin D supplementation	Positive effect on 25(OH)D and PTH levels
Song et al,[105] 2013	21 prospective studies	81,216	Healthy individuals and patients with type 2 diabetes	Circulating 25(OH)D	Association between blood levels of 25(OH)D and risk of incident type 2 diabetes	Inverse and significant association between circulating 25(OH)D levels and risk of type 2 diabetes
George et al,[106] 2012	15 trials	NA	Nondiabetes to diabetes	Vitamin D or analogues	Glycemia, insulin resistance, progression to diabetes, and complications of diabetes	No effect on fasting glucose, hemoglobin A_{1c} or insulin resistance Small positive effect on fasting glucose and insulin resistance in patients with diabetes or impaired glucose tolerance No effect on glycated hemoglobin in diabetic patients
Bath-Hextall et al,[107] 2012	11 studies	596	Atopic eczema/dermatitis	Vitamin D vs vitamin E	Treating established atopic eczema/dermatitis	Negative effect at high doses
Muir et al,[70] 2011	13 trials	NA	Older adults (≥60 y)	Vitamin D (800-1000 IU/d)	Muscle strength, gait, and balance	Positive effect on balance and muscle strength
Annweiler et al,[108] 2009	16 trials	24-33,067	Persons aged ≥80 y	NA	Muscle, balance, and gait performance	No significant effect on balance and gait Positive/no effect on muscle strength No effect on sit-to-stand test

Wang et al,[109] 2010	18 trials	NA	Adults	NA	Reduce the risk of cardiovascular events	No effect on cardiovascular disease risk
Pittas et al,[110] 2010	18 trials	37,162	Generally healthy adults	Vitamin D (400-8571 IU/d) with or without calcium	Cardiometabolic outcomes	No effect on glycemia or incident diabetes, blood pressure, and cardiovascular outcomes
Ferguson and Chang,[111] 2009	3 double-blind randomized crossover trials	41	Adults and children with cystic fibrosis	800 and 1600 IU of vitamin D alone with or without 1 g of calcium	Respiratory outcomes	No adequate evidence of benefit or harm
Abba et al,[112] 2008	12 trials	3393	Patients with tuberculosis	Several vitamins and minerals and diets	Promote the recovery of tuberculosis	No effect on number of deaths or number of participants with positive sputum test results
Autier and Gandini,[113] 2007	18 independent RCTs	57,311	At risk for dying of any cause	Vitamin D supplements varied from 300 to 2000 IU/d	Any health condition	Not enough evidence for effective decision

BMC = bone mineral content; BMD = bone mineral density; CKD = chronic kidney disease; HIV = human immunodeficiency virus; NA = not available; PTH = parathyroid hormone; RCT = randomized controlled trial; 25(OH)D =25-hydroxyvitamin D.

inducing cellular maturation, inducing apoptosis, and inhibiting angiogenesis while enhancing the expression of genes including *P21* and *P27* to control cellular proliferation (Figure 1).[1,2,7,16,26] Another vitamin D–regulated gene is *CYP3A4*, whose protein product detoxifies the bile acid lithocholic acid.[114] Lithocholic acid is believed to damage the DNA of intestinal cells, and it may promote colon carcinogenesis. Stimulating the production of a detoxifying enzyme by $1,25(OH)_2D$ could explain a protective role for improving vitamin D status against colon cancer.[114] Because vitamin D regulates a gamut of physiologic processes, including immune modulation, resistance to oxidative stress, and modulation of other hormones, it is not surprising that low vitamin D status has been associated with increased risk of several cancers and cancer mortality.[7,61,115-126] As the importance of noncoding RNAs has emerged, the ability of $1,25(OH)_2D$ to regulate microRNAs (miRNAs) has been found in several cancer cell lines, patient tissues, and sera. In vitamin D_3 intervention trials, significant differences in miRNAs were observed between treatment groups or between baseline and follow-up.[116] In patient sera from population studies, specific miRNA differences were associated with serum levels of 25(OH)D. The findings thus far indicate that increasing vitamin D_3 intake in patients and $1,25(OH)_2D_3$ in vitro not only regulates specific miRNA(s) but also up-regulates global miRNA levels.[116]

Epidemiologic studies have suggested that adequate levels of 25(OH)D are critical for the prevention of various solid tumors, including prostate, breast, ovarian, and colon cancers.[97,114,115,117-120] A meta-analysis for the US Preventive Services Task Force regarding vitamin D supplementation concluded that each 4-ng/mL increase in blood 25(OH)D levels was associated with a 6% reduced risk of colorectal cancer but not with statistically significant dose-response relationships for prostate and breast cancer.[97] In a large prospective study of lethal prostate cancer (1260 cases vs 1331 controls), men with the highest quartile of plasma 25(OH)D levels had less than half the risk of lethal prostate cancer compared with men with the lowest quartile of plasma 25(OH)D levels.[115] A meta-analysis including 1822 colon and 868 rectal cancers reported an inverse association

between circulating 25(OH)D levels and colorectal cancer, with a stronger association for rectal cancer.[97,121] Participants in the WHI who had a baseline 25(OH)D level less than 12 ng/mL and who took 400 IU of vitamin D_3 and 1000 mg of calcium daily had a 253% increased risk of colorectal cancer compared with women who took the same amount of vitamin D_3 and calcium for 7 years and had baseline serum 25(OH)D levels greater than 24 ng/mL.[84,122]

Although cross-sectional data have many limitations, the findings are hypothesis generating and can be used to develop protocols for RCTs.[84,123,124] The findings from prospective case-control cohort studies in which blood collection occurred many years before diagnosis add another dimension to the evidence.[118] The results of these studies generally support vitamin D supplementation in those with "low" vitamin D status. However, some have argued for caution before increasing 25(OH)D levels and associated dosing regimens beyond quantities clearly supported by RCTs and meta-analyses.[7,97,103] There are now several observational studies reporting a U- or J-shaped association between some cancers and serum 25(OH)D and latitude or UV-B radiation levels, in which those in the highest percentiles have an inverse risk compared with those in the lowest.[118,125-127] Many RCTs that were evaluated for nonskeletal benefits of vitamin D had problems with a high incidence of nonadherence, misinterpretation of the original data, and use of doses of vitamin D below the 2010 IOM recommendations.[62,123,124,128] A good example is the WHI.[129] More than 50% of participants in the WHI admitted not taking their calcium and vitamin D daily, and blood concentrations of 25(OH)D were often not measured at baseline or at study end.[124,129] Furthermore, the authors acknowledged that the 400 IU of vitamin D was inadequate to raise the blood level of 25(OH)D above 30 ng/mL, which most studies have suggested is required to reduce cancer risk and other nonskeletal acute and chronic diseases.[7,26,61,127,128] A reanalysis of the WHI concluded that in 15,646 women (43%) who were not taking personal calcium or vitamin D supplements at randomization, the calcium and vitamin D intervention significantly decreased the risk of total, breast, and invasive breast cancers by 14% to 20% and the risk of colorectal cancer by 17%.[84] In another RCT, a 60% reduction in all cancers was observed in postmenopausal women who ingested 1100 IU of vitamin D_3 and 1500 mg of elemental calcium daily for 4 years.[130] There is conflicting evidence about vitamin D's relationship with risk of pancreatic cancer. A study of more than 120,000 men and women from the Health Professionals Follow-up Study and the Nurses' Health Study found that participants with higher dietary intake of vitamin D had a progressively lower risk of pancreatic cancer compared with those who had the lowest intake.[131] In a study of men and women enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial,[132] no association between serum 25(OH)D levels and pancreatic cancer risk was observed. A pooled analysis of 5 nested case-control studies reported an inverse association between plasma levels of 25(OH)D and the subsequent risk of pancreatic cancer.[133] Compared with individuals with 25(OH)D levels less than 20 ng/mL, those with 25(OH)D levels of 20 ng/mL or greater experienced an approximately 30% lower risk of pancreatic cancer.

Grant[120,134,135] reported that more than 13 cancers were reduced by adequate exposure to solar UV-B radiation. He calculated that in a span of 24 years (1970-1994), 566,400 Americans died of cancer because of inadequate exposure to solar UV-B radiation.[120,134-136] He also estimated that 50,000 to 63,000 Americans and 19,000 to 25,000 British citizens in the United Kingdom die prematurely of cancer each year due to vitamin D deficiency.[135,136] A large collaborative effort analyzed data from 10 prospective cohort studies to examine whether serum 25(OH)D levels were associated with 7 rare cancers.[137] The National Cancer Institute Cohort Consortium Vitamin D Pooling Project of Rarer Cancers included information on serum 25(OH)D levels and the incidence of rare cancers in a subset of more than 12,000 men and women. The researchers matched participants on date and season of blood collection and used other statistical techniques to adjust for seasonal variation in serum 25(OH)D levels. When the data from the different studies were pooled, there was no overall association between vitamin D status and risk of non-Hodgkin lymphoma or cancers of the endometrium, esophagus, stomach,

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kidney, or ovary.[137] In contrast, a recent review of ecological studies associating solar UV-B exposure—vitamin D and cancers found strong inverse correlations with solar UV-B irradiance for 15 types of neoplasms: bladder, breast, cervical, colon, endometrial, esophageal, gastric, lung, ovarian, pancreatic, rectal, renal, and vulvar cancers and Hodgkin and non-Hodgkin lymphoma.[138] Weaker evidence was observed for 9 other types of cancer: brain, gallbladder, laryngeal, oral/pharyngeal, prostate, and thyroid cancers; leukemia; melanoma; and myeloma.[138] Although there was compelling evidence for the association between vitamin D intake and cancer risk, a meta-analysis by Buttigliero et al[98] found no effect of vitamin D supplementation on survival in patients with cancer.

Mortality

Vitamin D deficiency is associated with an increased risk of total mortality.[139] Most, but not all, studies documented increased mortality rates in patients with low 25(OH)D concentrations. In a study of 247,574 individuals from the primary care sector, a reverse J-shaped relation was reported between serum level of 25(OH)D and all-cause mortality, with the lowest mortality rate at 20 to 24 ng/mL.[126] This finding underscores the importance of not only including the very low (4 ng/mL) but also the higher (56 ng/mL) levels of 25(OH)D in the analysis.[126] It also raises several questions. How do patients who had a 25(OH)D level greater than 50 ng/mL attain such a high level, which is usually observed only in Africans living outdoors?[128,140] These people are likely taking megadoses of vitamin D and possibly other supplements or are being treated for vitamin D deficiency. In some instances, studies are misrepresented or misinterpreted. For example, the IOM reported in their overview that there was evidence of increased mortality for those with a 25(OH)D level greater than 30 ng/mL. However, one of the studies used to support this IOM conclusion actually stated that mortality rates were reduced until the blood level of 25(OH)D reached 50 ng/mL and that mortality rates possibly increased only in women who had 25(OH)D levels greater than 50 ng/mL.[141] When these J curves are plotted, we are not informed what percentage of study participants had a 25(OH)D level greater than 50 ng/mL. By some estimates, less than 10% of patients have a 25(OH)D level greater than 50 ng/mL, and in a recent meta-analysis,[126] only 1.5% of participants had a 25(OH)D level greater than 50 ng/mL. This raises questions about the validity of the so-called J-U curve analyses.

A meta-analysis of prospective cohort studies including 5562 deaths of 62,548 participants suggested a nonlinear decrease in mortality risk as circulating 25(OH)D concentration increases, with optimal outcomes occurring at concentrations of approximately 30 to 35 ng/mL.[142] In a similar meta-analysis, vitamin D intake and blood 25(OH)D levels were inversely associated with risk of colorectal cancer, and a 10-ng/mL increase in blood 25(OH)D levels conferred a risk rate (RR) of 0.74.[143] A meta-analysis of prospective studies of 6853 patients with chronic kidney disease found that the mortality risk decreased by 14% per 10-ng/mL increase in 25(OH)D levels.[144] The major cause of mortality was cardiovascular disease.

In a recent meta-analysis with 70,528 randomized participants (86.8% females) with a median age of 70 years, vitamin D supplementation with or without calcium reduced mortality by 7%. However, vitamin D supplementation alone did not affect mortality, but risk of death was reduced if vitamin D was given with calcium.[145] The Ludwigshafen Risk and Cardiovascular Health Study is a cohort study of patients referred for coronary angiography between 1997 and 2000, from which 1801 with the metabolic syndrome were investigated. Mortality was tracked for a median of 7.7 years.[146] Multivariable survival analysis was used to estimate the association between serum 25(OH)D levels and mortality. After full adjustment, including the metabolic syndrome components, patients with optimal 25(OH)D levels had a substantial reduction in all-cause (hazard ratio [HR], 0.25; 95% CI, 0.13-0.46) and cardiovascular disease (HR, 0.33; 95% CI, 0.16-0.66) mortality rates compared with those with severe vitamin D deficiency. For specific cardiovascular disease mortality, there was a strong reduction in sudden death (HR, 0.15; 95% CI, 0.04-0.63) and congestive heart failure (HR, 0.24; 95% CI, 0.06-1.04) but not for myocardial infarction. The reduction in the mortality rate was dose dependent for each of these causes.[146] Consistent with the beneficial effect of vitamin D on risk of mortality, a meta-analysis of 50

randomized trials by Bjelakovic et al[99] found a positive effect of vitamin D_3 on mortality.

Cardiovascular Disorders and Type 2 Diabetes Mellitus

Observational studies in humans found that 25(OH)D and $1,25(OH)_2D$ levels are inversely related to coronary artery calcifications[147,148] and are lower in patients with myocardial infarction.[149] An in vitro study suggested that low 25(OH)D levels influence the activity/expression of macrophages and lymphocytes in atherosclerotic plaques, thus promoting chronic inflammation in the artery wall.[150] Additionally, $1,25(OH)_2D_3$ inhibited foam cell formation and promoted angiogenesis in endothelial colony-forming cells in vitro, possibly due to an increase in vascular endothelial growth factor expression and pro–matrix metalloproteinase-2 activity.[4,151] A short course of treatment with vitamin D (4000 IU for 5 days) effectively attenuated the increase in circulating levels of inflammatory cytokines after an acute coronary event.[150] These findings provide support for the anti-inflammatory effects of vitamin D on the vascular system and suggest mechanisms that mediate some of its cardioprotective properties.[4,150] In addition, low 25(OH)D concentrations result in elevations in PTH levels, which have been linked to insulin resistance and significant increases in the serum levels of many acute phase proteins.[149]

Wang et al[152] studied 1739 Framingham Offspring Study participants (mean age, 59 years; 55% women; all of white race) without previous cardiovascular disease. During mean follow-up of 5.4 years, 120 individuals experienced a first cardiovascular event. Individuals with 25(OH)D levels less than 15 ng/mL had a multivariable-adjusted HR of 1.62 for incident cardiovascular events compared with those with 25(OH)D levels of 15 ng/mL or greater. This effect was evident in participants with hypertension (HR, 2.13; 95% CI, 1.30-3.48) but not in those without hypertension.[152] Observational studies indicated that a serum 25(OH)D level less than 30 ng/mL was strongly associated with hypertension and metabolic syndrome.[153] This effect is thought to be partly mediated through regulation of the renin-angiotensin-aldosterone axis.[154] The Intermountain Heart Collaborative Study Group prospectively analyzed a large electronic medical records database that contained 41,504 patient records. Serum 25(OH)D levels less than 30 ng/mL were associated with highly significant increases in the prevalence of diabetes, hypertension, hyperlipidemia, and peripheral vascular disease. Serum 25(OH)D levels were also highly associated with coronary artery disease, myocardial infarction, heart failure, and stroke and with incident death, heart failure, coronary artery disease/myocardial infarction, stroke, and their composite.[153] Black normotensive children who received 2000 IU/d of vitamin D_3 were compared with those who received 400 IU/d for 16 weeks in an RCT. Teenagers who received 400 IU/d of vitamin D_3 increased their mean ± SD plasma levels of 25(OH)D from 13.6±4.2 to 23.9±7.2 ng/mL and had no reduction in arterial wall stiffness. In contrast, teenagers who received 2000 IU/d of vitamin D_3 increased their mean ± SD plasma levels of 25(OH)D from 13.2±3.4 to 34.2±12.1 ng/mL and significantly lowered their arterial wall stiffness.[155] This finding is supported by the observation that serum 25(OH)D levels less than 30 ng/mL were strongly associated with hypertension, elevated blood glucose, and metabolic syndrome in adolescents.[156] Children with vitamin D deficiency or insufficiency had a 2.5-fold higher risk of an elevated blood glucose level, a 2.4-fold increased risk of elevated blood pressure, and a 4-fold increased risk of metabolic syndrome, a prelude to type 2 diabetes.[156]

A meta-analysis of 11 prospective studies involving 3612 cases and 55,713 noncase participants provided the largest and most comprehensive assessment thus far of the association between circulating 25(OH)D levels and type 2 diabetes. It suggested a strong inverse association between serum 25(OH)D concentration and incidence of type 2 diabetes. The combined RR of 0.59 suggested that the risk of future diabetes may be reduced by 41% (95% CI, 33%-48%) by having a serum 25(OH)D level greater than 32 ng/mL compared with a serum 25(OH)D level less than 19.5 ng/mL at baseline.[157] The MIDSPAN family study was a prospective study of 1040 men and 1298 women from the West of Scotland recruited in 1996 and followed up for a median of 14.4 years.[158] Plasma levels of 25(OH)D less than 15 ng/mL were not associated with a risk of cardiovascular disorders in this cohort with very low 25(OH)D levels. The median plasma 25(OH)D level was 18.6 ng/mL, and the median vitamin D intake was 3.2 μg/d

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(128 IU/d). However, there was some evidence that a 25(OH)D level less than 15 ng/mL was associated with all-cause mortality.[158] There was an association between 25(OH)D levels and incidence of type 2 diabetes, but there was no evidence in this study of a beneficial effect of vitamin D supplementation on type 2 diabetes outcomes.[106] A meta-analysis of 15 trials by George et al[106] did not find sufficient evidence to recommend vitamin D supplementation for improving glycemia or insulin resistance in patients with diabetes, normal fasting glucose levels, or impaired glucose tolerance. Similarly, Wang et al[109] and Pittas et al[110] concluded in their meta-analyses that evidence from limited data suggested that vitamin D supplements at moderate to high doses may reduce the risk of cardiovascular disease,[109] but most studies that used lower doses found no clinically meaningful effect.[110]

Autoimmune Diseases

Vitamin D has been defined as a natural immune modulator. Epidemiologic, genetic, and basic science studies indicate a potential role of vitamin D in the pathogenesis of certain systemic and organ-specific autoimmune diseases, such as type 1 diabetes mellitus, MS, rheumatoid arthritis (RA), and Crohn disease (CD).[159] Vitamin D's effects on the innate immune system are predominantly through the toll-like receptors and on the adaptive immune system through T-cell differentiation, particularly the T helper cell (T_H) type 17 response. Because T_H17 cells are critical in the pathogenesis of RA, this has led to an interest in the effects of vitamin D deficiency in RA.[160] Vitamin D inhibits immune reactions in general, but it enhances the transcription of endogenous antibiotics, such as cathelicidin and defensins.[26,161] Vitamin D suppresses autoimmune disease pathology by regulating the differentiation and activity of $CD4^+$ T cells, resulting in a more balanced T_H1/T_H2 response that favors less development of self-reactive T cells and autoimmunity.[162] The T_H1-dependent autoimmune diseases, including MS, type 1 diabetes, CD, and RA, are also inhibited by $1,25(OH)_2D_3$ owing to inhibition of antigen presentation, reduced polarization of T_H0 cells to T_H1 cells, and reduced production of cytokines from the latter cells.[161] The $1,25(OH)_2D_3$ down-regulated the proinflammatory cytokine (interleukin 1β, interleukin 6, and tumor necrosis factor) production in human activated macrophages by significantly decreasing the aromatase activity, especially in the presence of an estrogenic milieu, such as in RA synovial tissue.[163] A prospective cohort study of 29,368 women aged 55 to 69 years without a history of RA found an inverse association between vitamin D intake and RA after 11 years of follow-up.[164] There was a 34% reduction in the development of RA with greater vitamin D intake. Women using a multivitamin with 400 IU of vitamin D reduced their risk of RA by 40%.[164] Use of a high-dose vitamin D_3 analogue resulted in improvement of symptoms of RA in 89% of patients, with 45% of patients entertaining a complete remission.[165] Recent evidence has suggested a significant inverse relationship between serum 25(OH)D levels and visual analog scale scores in patients with RA.[166] Very low serum 25(OH)D levels (≤6 ng/mL) were characterized by patients being positive for rheumatoid factor, a high percentage of patients with very high disease activity, and a high percentage of patients requiring treatment with at least 3 disease-modifying antirheumatic drugs.[167]

There is a large body of evidence linking a lack of vitamin D early in life to the development of type 1 diabetes.[168] Vitamin D supplementation during infancy was reported to confer partial protection against β-cell autoimmunity.[169] There is consistent evidence from observational studies for potential long-term programming effects of vitamin D supplementation on immunologic diseases, such as type 1 diabetes, MS, asthma, and allergic diseases.[5] There was a 63% decreased risk of islet cell antibodies in offspring with a single standard deviation (156 IU) increase in recalled maternal dietary vitamin D intake during pregnancy.[5] Similarly, higher maternal cod liver oil (a source of vitamin D) intake during pregnancy was associated with a decreased risk of type 1 diabetes in offspring, and fetal exposure to vitamin D deficiency was linked to a higher metabolic and cardiovascular disease risk in adult life.[170]

A Finnish study (10,366 children) found that children who regularly took the recommended dose of vitamin D (2000 IU/d) had a rate ratio of 0.22 (95% CI, 0.05-0.89) compared with those who regularly received less than the recommended amount.[171] The $1,25(OH)_2D_3$ has been reported in animal models and in cultured cells to improve insulin production, modulate T- and β-cell activity, enhance phagocytic killing activity, improve vascular smooth muscle resistance, and

reduce the risk of autoimmune diseases.[7,155,162] In contrast, in healthy youth (aged 8-18 years), plasma 25(OH)D concentrations had no independent relationship with parameters of glucose homeostasis and in vivo insulin sensitivity and β-cell function relative to insulin sensitivity.[172] It remains to be determined whether in youth with dysglycemia the relationships are different and whether vitamin D optimization enhances insulin sensitivity and β-cell function.[172]

Evidence continues to accumulate supporting a protective role for vitamin D in MS risk and progression. Notable recent findings are that high 25(OH)D levels at the time of a first demyelinating event predicts a lower MS risk and a decreased risk of MS in offspring whose mothers had high 25(OH)D levels.[173] An American study of more than 187,000 women followed up for 10 to 20 years reported promising results with women taking at least 400 IU of supplemental vitamin D daily. The risk of MS was decreased by 41%.[174] An epigenetic study in lymphoblastoid cell lines reported relevant insights into how vitamin D may influence the immune system and the risk of MS through VDR interactions with the chromatin state inside MS-associated genomic regions.[175] Higher 25(OH)D levels were associated with decreased exacerbation risk in relapsing-remitting MS.[175] However, the literature is limited by small study sizes, heterogeneity of dosing, form of vitamin D tested, and clinical outcome measures.[176] Whether vitamin D_3 immunomodulatory effects can be translated into clinical benefits in patients with MS is still a matter of debate.[176] High doses of vitamin D_3 (up to 280,000 IU/wk for 6 weeks) have been used safely in patients with MS.[177,178] Blood levels of 25(OH)D rose to a mean of 154 ng/mL without causing hypercalcemia. The progression and activity of MS were not affected in this study, but the number of gadolinium-enhancing lesions per patient assessed by nuclear magnetic brain scan was significantly reduced.[177] A trial using high-dose vitamin D_2 to achieve 25(OH)D levels of 52 to 78 ng/mL did not reduce magnetic resonance imaging lesions in relapsing-remitting MS.[178] In a trial using escalating doses up to 40,000 IU/d of vitamin D_3 for 28 weeks followed by 10,000 IU/d for 12 weeks, there were no significant adverse events, and there seemed to be significantly less progression of disability in the treatment group.[179]

A chromatin immunoprecipitation sequencing–defined genome-wide map of VDR binding reported that there were 2776 "binding sites" on the human genome with at least 229 genes associated with type 1 diabetes and CD.[180] In a clinical trial in patients with CD in remission, 1200 IU of vitamin D_3 daily increased mean ± SD serum 25(OH)D levels from 27.6±12.4 to 38.4±10.8 ng/mL after 3 months.[181] The relapse rate was numerically lower in patients treated with vitamin D_3 (6 of 46 or 13%) than in patients treated with placebo (14 of 48 or 29%), although this did not quite reach significance (P=.06). Monocyte-derived dendritic cells (DCs) from 20 patients with CD were cultured with either 25(OH)D_3 or 1,25$(OH)_2D_3$ and were matured with lipopolysaccharide (LPS).[182] After stimulation with 25(OH)D_3, DCs from patients with CD displayed a reduced response to LPS with a diminished capability to activate T cells compared with DCs stimulated with LPS alone. Compared with LPS alone, both metabolites of vitamin D_3 reduced the ability of DCs to activate lymphocytes. These data indicate that intrinsic activation of 25(OH)D_3 to 1,25$(OH)_2D_3$ occurs in DCs from patients with CD and provides evidence that higher serum 25(OH)D_3 levels can potentially modulate DC function in CD.[182] Although several studies reported the immunomodulatory effects of vitamin D on biological functions and developing processes of autoimmune diseases, there is no strong evidence for recommending vitamin D supplementation to prevent or manage the autoimmune diseases on the basis of the results of some short-term clinical trials.[177,178,181]

Respiratory Tract Diseases and Wheezing Disorders

At the turn of the past century, children with rickets were at higher risk for upper respiratory tract infections and for dying of them.[26,183] Macrophages have a VDR, and when they ingest an infectious agent, such as tuberculosis bacillus, the toll-like receptors are activated, resulting in signal transduction to increase the expression of VDR and *CYP27B1*.[7,26,28] In turn, 25(OH)D is converted to 1,25$(OH)_2D$, which signals the nucleus to increase the expression of cathelicidin, a defensin protein that kills infective agents, such as tuberculosis bacillus.[7,26,28]

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Cord blood 25(OH)D levels were associated with tolerogenic immune regulation and fewer respiratory tract infections in newborns.[184] Also, high 25(OH)D levels during maternity were associated with a decrease in childhood wheezing by nearly 50% compared with low maternal 25(OH)D levels. Newborns with 25(OH)D levels less than 10 ng/mL were twice as likely to develop respiratory tract infections compared with those with levels of 30 ng/mL or greater, and every 4-ng/mL increase in the cord blood 25(OH)D level lowered the cumulative risk of wheezing by age 5 years.[184] Serum concentrations of 25(OH)D in 198 healthy adults revealed that a concentration of 38 ng/mL or higher reduced the risk of acute viral respiratory tract infections and number of days ill by 2-fold.[185] Japanese children who received 1200 IU/d of vitamin D from December through March compared with those who received placebo reduced their risk of influenza A by 42%.[186] It was also observed that children who took vitamin D daily had a relative risk reduction of 93% for having an asthma attack compared with children who did not take a vitamin D supplement.[186] Vitamin D has also been implicated in the reversal of corticosteroid resistance and in airway remodeling, which are the hallmarks of chronic obstructive pulmonary disease and severe asthma. Dietary vitamin D may regulate epigenetic events, in particular on genes that are responsible for chronic obstructive pulmonary disease susceptibility.[187]

The potential role of vitamin D in reducing the risk of allergies also may be related to epigenetic regulation.[188,189] Misdirected epigenetic programming offered an explanation for why vitamin D deficiency in pregnancy may be associated with increased allergy rates in the offspring. The cord blood level of 25(OH)D found a U-shaped association, with a 2.4-fold odds ratio (OR) of low and a 4-fold OR of high levels of 25(OH)D to develop allergen-specific IgE.[188,190] Eczema was significantly more likely in those with 25(OH)D levels less than 20 ng/mL compared with those with 25(OH)D levels of 30 ng/mL or greater (OR, 2.66; 95% CI, 1.24-5.72; P=.01).[189] On a molecular level, maternal vitamin D intake during pregnancy increased the messenger RNA levels of immunoglobulin-like transcript (ILT) 3 and ILT4 in umbilical cord blood.[191] Because ILT3 and ILT4 are critical for the generation of T suppressor cells and the induction of immunologic tolerance, this finding may point toward an early induction of tolerogenic immune responses by maternal vitamin D intake in the developing child. In addition, vitamin D stimulates natural killer cells that are known to play an immunoregulatory role in the prevention of autoimmune diseases.[2] Thus, although vitamin D can favorably influence several pathways associated with respiratory tract diseases, there are few clinical trials to support the beneficial effect of vitamin D supplementation for these patients. Meta-analyses on respiratory outcomes[111] and recovery from tuberculosis[112] did not report a beneficial effect of supplementation for patients with cystic fibrosis or tuberculosis, respectively.

Neurologic Disorders

The brain has a VDR and has the ability to produce $1,25(OH)_2D_3$. In vivo mouse studies found that in utero hypovitaminosis D impairs brain development and leads to persistent changes in the adult brain.[192] The $1,25(OH)_2D_3$ is rapidly incorporated into embryonic hippocampal cells, moves into the nucleus, and then returns to the cytoplasm.[193] These events delay cell proliferation and induce cell differentiation characterized by the expression of differentiation markers, modification of soma lengthening, and increase in neurite length and branching.[193] At birth, rats with prenatal vitamin D deficiency had heavier and longer brains, enlarged lateral ventricles, and decreased cortical thickness.[5,192,194-196] Evidence from human studies is scanty. One recent study found that higher maternal serum 25(OH)D levels in late pregnancy (<12 vs >30 ng/mL) were associated with larger head circumference of offspring at 9 years old but not with measures of cognition or psychological health.[5,194] In addition, there may be a critical window during late gestation in which vitamin D insufficiency precipitates an altered adult behavioral phenotype.[195] In rats, offspring of vitamin D–deficient mothers had significant impairment of latent inhibition (ability to ignore irrelevant stimuli), a feature often associated with schizophrenia, whereas those transiently depleted had subtle and discrete alterations in learning and memory.[196] In a Finnish birth cohort study, 9114 individuals were drawn from the northern Finland 1966 birth cohort.[197] In males, the use of at least 2000 IU of vitamin D during the first year of life was associated with a

reduced risk of schizophrenia (RR, 0.23; 95% CI, 0.06-0.95) compared with those taking lower doses.[197]

There is minimal evidence for an association of low maternal vitamin D status with risk of autism.[5] Children of dark-skinned mothers, particularly immigrants to locations with low ambient UV radiation, such as Minnesota, may be at increased risk, but this finding has been inconsistent.[198]

The $1,25(OH)_2D_3$ seems to have a neuroprotective role, inducing remyelination by endogenous progenitor cells and stimulation of amyloid-β clearance by macrophages of patients with Alzheimer disease.[199] A vitamin D_3–enriched diet correlated with a decrease in the number of amyloid plaques and inflammation in the brains of AβPP mice.[199] These observations suggest that a vitamin D_3–enriched diet may reduce the risk of Alzheimer disease as well as depression and neurocognitive disorders. An Australian study of 743 white pregnant women found that maternal vitamin D insufficiency during pregnancy is significantly associated with offspring language impairment.[200] Vitamin D deficiency was also associated with prominent changes in behavior and brain neurochemistry in the adult mouse.[201] In the follow-up of a British birth cohort (n=7401), current and subsequent risk of depression in middle adulthood was associated with low serum 25(OH)D levels.[202] This study provides support for a lower risk of depression with serum 25(OH)D levels between 20 and 34 ng/mL. A meta-analysis of cohort studies reported that there was a significantly increased HR of depression for the lowest vs highest vitamin D categories (HR, 2.21; 95% CI, 1.40-3.49).[203] In a community setting, depressed adults had significantly lower 25(OH)D levels than those without depression.[204] A variety of studies found an association between a low level of 25(OH)D and a high depression score.[205,206] Patients who received 400 to 800 IU of vitamin D with calcium for 6 to 12 months did not have an improvement in their mental health scores. However, patients who received 400 to 800 IU of vitamin D for 5 days with calcium or a single 100,000-IU dose of vitamin D had an improvement in the assessments of depression.[207,208] Although there is a strong association between risk of neurologic disorders and serum 25(OH)D concentrations, there are only a few short-term clinical trials of vitamin D in patients with MS that have not reported benefit and no clinical trials evaluating other neurologic disorders.[177,178]

Adverse Pregnancy Outcomes

A recent meta-analysis of data from 24 studies found that women with circulating 25(OH)D levels less than 20 ng/mL in pregnancy experienced an increased risk of preeclampsia (OR, 2.09; 95% CI, 1.50-2.90), gestational diabetes mellitus (OR, 1.38; 95% CI, 1.12-1.70), preterm birth (OR, 1.58; 95% CI, 1.08-2.31), and small-for-gestational-age (OR, 1.52; 95% CI, 1.08-2.15).[209] However, many of these outcomes are rare and require a large sample size to study, representing a challenge for cohorts with a limited number of preserved samples. Experimental studies have provided evidence of disrupted vitamin D metabolic homeostasis in the preeclamptic placenta and have suggested that increased oxidative stress could be a causative factor of altered vitamin D metabolism in preeclamptic placentas.[50] In normal placenta, DBP, *CYP24A1*, and VDR expressions were localized mainly in trophoblasts, whereas *CYP2R1* and *CYP27B1* expressions were localized mainly in villous core fetal vessel endothelium.[50] Protein expression of *CYP2R1* and VDR were reduced, but *CYP27B1* and *CYP24A1* expressions were elevated in preeclamptic compared with normotensive placentas.[50] A similar pattern was observed in an in vitro model that found that hypoxia induced down-regulation of DBP, *CYP2R1*, and VDR and up-regulation of *CYP27B1* and *CYP24A1*.[50] These data indicate that fetal (trophoblastic) autocrine synthesis of $1,25(OH)_2D_3$ may play a pivotal role in controlling placental inflammation and preeclampsia.

One of the main pathogenic features of preeclampsia is maternal endothelial dysfunction that results from impaired angiogenesis and reduced endothelial repair capacity. The $1,25(OH)_2D_3$ improves the angiogenic properties of endothelial progenitor cells. These findings could explain the positive influence of vitamin D_3 in reducing preeclampsia risk.[151]

There was an inverse association with having a cesarean delivery and serum 25(OH)D levels. In a case-control study, after adjustment for race, age, educational level, insurance status, and alcohol use, women with 25(OH)D levels less than 15 ng/mL were

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almost 4 times as likely to have a cesarean delivery than were women with 25(OH)D levels of at least 15 ng/mL.[210]

A meta-analysis of 3 trials involving 463 women suggested that women who received vitamin D supplements during pregnancy less frequently had a baby with a birth weight less than 2500 g than did those who received no treatment or placebo; the statistical significance was borderline.[89] In terms of other conditions, there were no significant differences in adverse effects, including nephrotic syndrome, stillbirths, and neonatal deaths, between women who received vitamin D supplements and women who received no treatment or placebo.[89] A meta-analysis indicated a significant inverse relation between serum 25(OH)D level and the incidence of gestational diabetes mellitus. Overall, vitamin D deficiency (25[OH]D <20 ng/mL) in pregnancy was significantly related to the incidence of gestational diabetes mellitus, with an OR of 1.61.[211] However, it remains unclear whether this association is causal owing to the observational design of the studies. Recently, meta-analyses by Thorne-Lyman and Fawzi[88] and De-Regil et al[89] reported a similar beneficial effect of vitamin D supplementation on birth weight but no significant effect on other maternal and neonatal outcomes.

ASSESSING VITAMIN D STATUS

Although the generally accepted measure of vitamin D status is circulating 25(OH)D concentration, there is little consensus on which assay method should be used. Commonly used assays include competitive protein-binding assay, radioimmunoassay, enzyme immunoassay, chemiluminescence immunoassay, high-performance liquid chromatography, and liquid chromatography–tandem mass spectrometry (LC-MS/MS), each with its own advantages and disadvantages.[212,213] Binkley et al[214] reported that 25 (OH)D results differed widely depending on the laboratory and the method used, with the mean result (from 10 healthy adults) varying from 17.1 to 35.6 ng/mL. A study conducted by the Vitamin D External Quality Assessment Scheme found a 31% overestimation by one immunoassay method.[215] Its specificity needs to exclude significant interferences from the C-3 epimer of 25(OH)D, which is more prevalent in infants younger than 1 year.[216]

DiaSorin radioimmunoassays (DiaSorin Corp) used in the NHANES III had a mean bias of greater than 12% comparing the vitamin D status of the US population of 1988-1994 with that of 2000-2004. This difference was probably caused by changes in reagents and calibration lots performed by the manufacturer.[217,218] This makes diagnostic and therapeutic decisions on the basis of absolute cutoff values for vitamin D deficiency extremely problematic[219,220] and hinders the comparability of results from prospective and epidemiologic studies. Since November 2010, efforts have been made to recalibrate 25(OH)D measurements from all NHANES samples with LC-MS/MS. This effort is within the context of an international approach to standardization of 25(OH)D measurements in national surveys, the Vitamin D Standardization Program, and publication of the results is planned for the middle of 2013.[221] To ensure that laboratories are providing accurate testing results, it is important that their vitamin D testing method measures total 25(OH)D levels [$25(OH)D_2$ and $25(OH)D_3$] and has acceptable precision. The immunoassay remains the predominant mode of measurement for 25(OH)D. Most, if not all, of these assays have problems with equimolar recovery of the $25(OH)D_2$ and $25(OH)D_3$ levels.[222] The level of $25(OH)D_2$ is underestimated by 20% to 80% and can vary for different patients who received vitamin D_2 in the same assay. Standardization of all assays has been improved but not resolved with the currently available reference materials, as evidenced by the Vitamin D External Quality Assessment Scheme.[222] The choice of method for each laboratory remains a balance mainly among turnaround time, convenience, cost, and the specificity and accuracy of the information obtained.[208] Recognizing the importance of a $25(OH)D_2$ and $25(OH)D_3$ reference material, the National Institute of Standards and Technology released a 4-level Standard Reference Material set, SRM972.[221] Treatment with vitamin D_2, therefore, may not be accurately monitored using many of the commercial assays because these antibody assays often underestimate $25(OH)D_2$ levels and, thus, total 25(OH)D levels, which is what they record in the report. This issue is most important in patients who experience no improvement with replacement therapy with vitamin D_2 (the most

commonly used Food and Drug Administration–approved pharmaceutical form of vitamin D); the absence of a rise in the total 25(OH)D level may indicate nonadherence or malabsorption.[223] For these patients, use of the gold standard LC-MS/MS would quantitatively report 25(OH)D_2, 25(OH)D_3, and total 25(OH)D levels.

VITAMIN D STATUS DURING PREGNANCY, BIRTH, AND CHILDHOOD

Maternal vitamin D deficiency predisposes to low vitamin D stores in the newborn and increases infantile rickets[224] because the mother is the only source of vitamin D during pregnancy. The prevalence of vitamin D deficiency and insufficiency during pregnancy is of special concern and ranges from 8% to 100%, depending on the country of residence and the definitions of vitamin D deficiency and insufficiency (Figure 5).[2] In the United States, vitamin D deficiency and insufficiency is estimated to be 27% to 91% in pregnant women.[2] As shown in Figure 5, this rate is estimated to be 36% to 65% in Canada, 45% to 98% in Asia, 70% to 100% in Europe, and 25% to 65% in Australia and New Zealand.[124,128]

The prevalence of vitamin D deficiency and insufficiency in children in China is high, especially in children aged 6 to 16 years.[211] In the United States, it is estimated that 50% of children aged 1 to 5 years and 70% of children aged 6 to 11 years are vitamin D deficient or insufficient.[156] Recent studies reported that adolescents and young adults are also at risk for vitamin D deficiency.[16,128,217] Also, a high prevalence of vitamin D deficiency was reported in a cross-sectional study conducted at a tertiary care center in western India.[225]

Evidence suggests that children and adults in the United States are becoming more vitamin D deficient and insufficient because of an increase in the incidence of obesity, a decrease in milk consumption, and an increase in sun protection.[15,217] This recent evidence emphasizes the high prevalence of vitamin D deficiency throughout the world, not only in at-risk groups (Figure 5).[7,15,217,224-230]

PREVALENCE OF VITAMIN D DEFICIENCY IN ADOLESCENTS AND ADULTS

It has been estimated that 20% to 80% of US, Canadian, and European men and women are vitamin D deficient.[228,229] The prevalence of serum 25(OH)D levels less than 20 ng/mL was almost one-third of the US population (32%).[217] More than 70% of non-Hispanic black individuals and more than 40% of Hispanic/Mexican individuals were at risk for a 25(OH)D level less than 20 ng/mL.[228] In a national Canadian cohort, serum 25(OH)D levels less than 30 ng/mL were evident in 57.5% of men and in 60.7% of women, and they rose to 73.5% in spring (men) and 77.5% in winter (women).[229] In the Healthy Lifestyle in Europe by Nutrition in Adolescence study, 25(OH)D levels less than 30 ng/mL were reported to be approximately 80% in adolescents from the 9 European countries.[230] Levels of 25(OH)D were higher in northern Europe than in southern Europe and were higher in western Europe than in eastern Europe.[230] The higher levels in northern Europe were also observed in some multicenter studies in which a single laboratory facility was used.[230]

The higher serum 25(OH)D levels in Norway and Sweden are probably due to a high intake of fatty fish and cod liver oil. The lower serum 25(OH)D levels in Spain, Italy, and Greece may be due to more skin pigmentation, sunshine-avoiding behavior, and air pollution with ozone and nitrogen dioxide, which reduce sun-induced vitamin D production.[226]

In the Middle East and Asia, vitamin D deficiency in children and adults is highly prevalent.[7,227] Children and adults of color are especially at high risk owing to the inefficient cutaneous production of vitamin D_3.[1,2,7] In a study on the vitamin D status of Australian adults, vitamin D deficiency (25[OH]D <20 ng/mL) was 31% (22% in men and 39% in women); 73% had 25(OH)D levels less than 30 ng/mL.[226] Women who practice purdah (ie, the use of clothing and other approaches to screen themselves from men and strangers) and children and adults who avoid all sun exposure or wear sunscreen protection are equally at high risk.[7,231]

CAUSES OF VITAMIN D DEFICIENCY AND RISK FACTORS

Traditional risk groups for vitamin D deficiency include pregnant women, children, older persons, the institutionalized, and non-Western immigrants.[7,228] The major source of vitamin D for children and adults is exposure to natural sunlight.[7,61] The Maasai and

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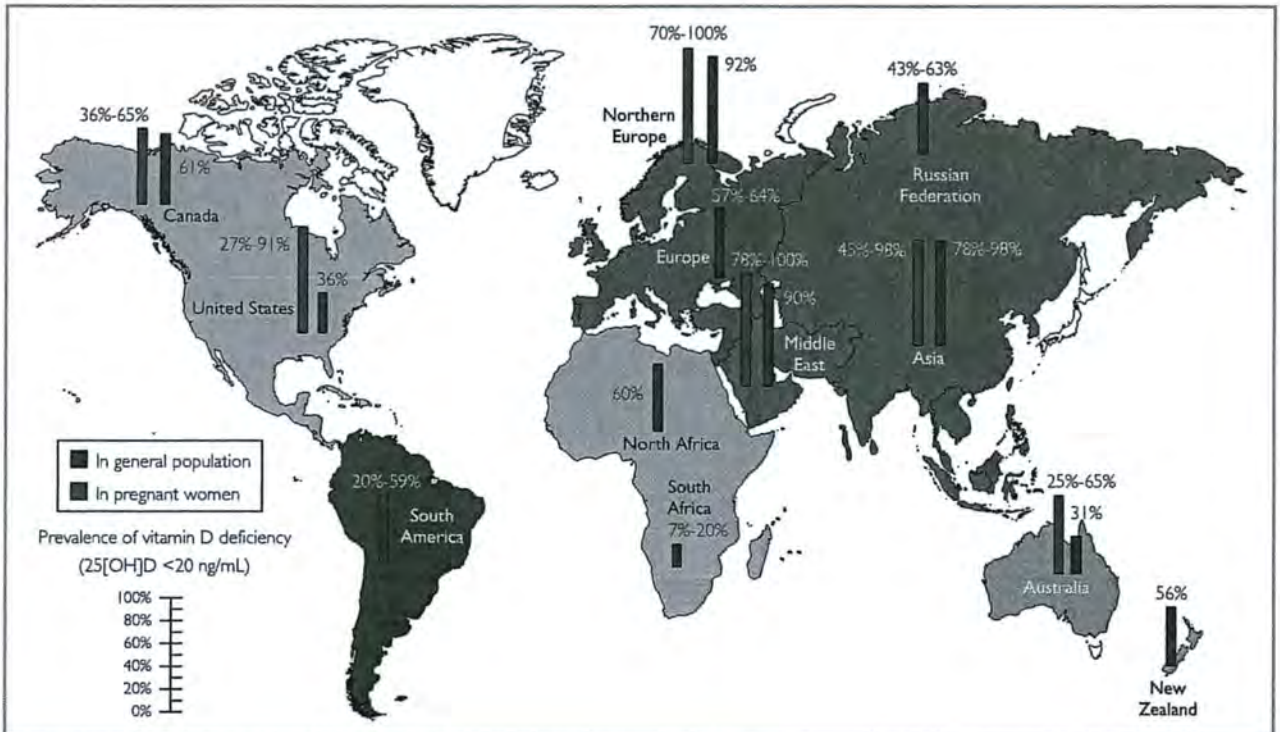

FIGURE 5. Reported incidence of vitamin D deficiency defined as a 25-hydroxyvitamin D (25[OH]D) level below 20 ng/mL around the globe in pregnant women and the general population. To convert 25(OH)D values to nmol/L, multiply by 2.496. Copyright Holick 2013, reproduced with permission.

Hadzabe tribes in Tanzania (East Africa) with traditional lifestyles, living in the presumed cradle of humankind, who are exposed daily to tropical sunlight had a mean circulating 25(OH)D level of 46 ng/mL.[140]

A variety of factors influence the cutaneous production of vitamin D. A sunscreen with a sun protection factor of 30 applied properly reduces the ability of the skin to produce vitamin D by as much as 95% to 99%. People of color who have natural sunscreen protection from their increased melanin pigment are less efficient by more than 90% in producing vitamin D in their skin compared with white individuals.[232] In addition, air pollution with increased ozone and nitrogen dioxide levels (both known to compromise several health outcomes) absorbs UV-B radiation and is an often-neglected risk factor for hypovitaminosis D.[61,233] Important risk factors for vitamin D deficiency are shown in Figure 6.

The prevalence of vitamin D deficiency and insufficiency is affected by seasonal variation and latitude. The prevalence increases in late winter/spring and decreases in summer.[234] A study of the effect of education on vitamin D status found that low-educated women had lower 25(OH)D levels compared with high-educated women, and women in the lowest 25(OH)D quartile had a higher risk of small-for-gestational-age offspring.[235]

The elderly population is particularly at risk for clinical complications related to low 25(OH)D levels. With increasing age, solar exposure is usually limited because of changes in lifestyle factors, such as clothing and less outdoor activity. Diet may also become less varied, with a lower natural vitamin D content. Most important, however, the cutaneous production of vitamin D after exposure to solar UV-B radiation decreases with age because of atrophic skin changes, with a reduced amount of its precursor 7-DHC.[236,237] A comparison of the amount of previtamin D_3 produced in skin from 8- to 18-year-old individuals with the amount produced in skin from 77- to 82-year-old individuals revealed that aging can decrease by greater than 2-fold the capacity of the skin to produce previtamin D_3.[237]

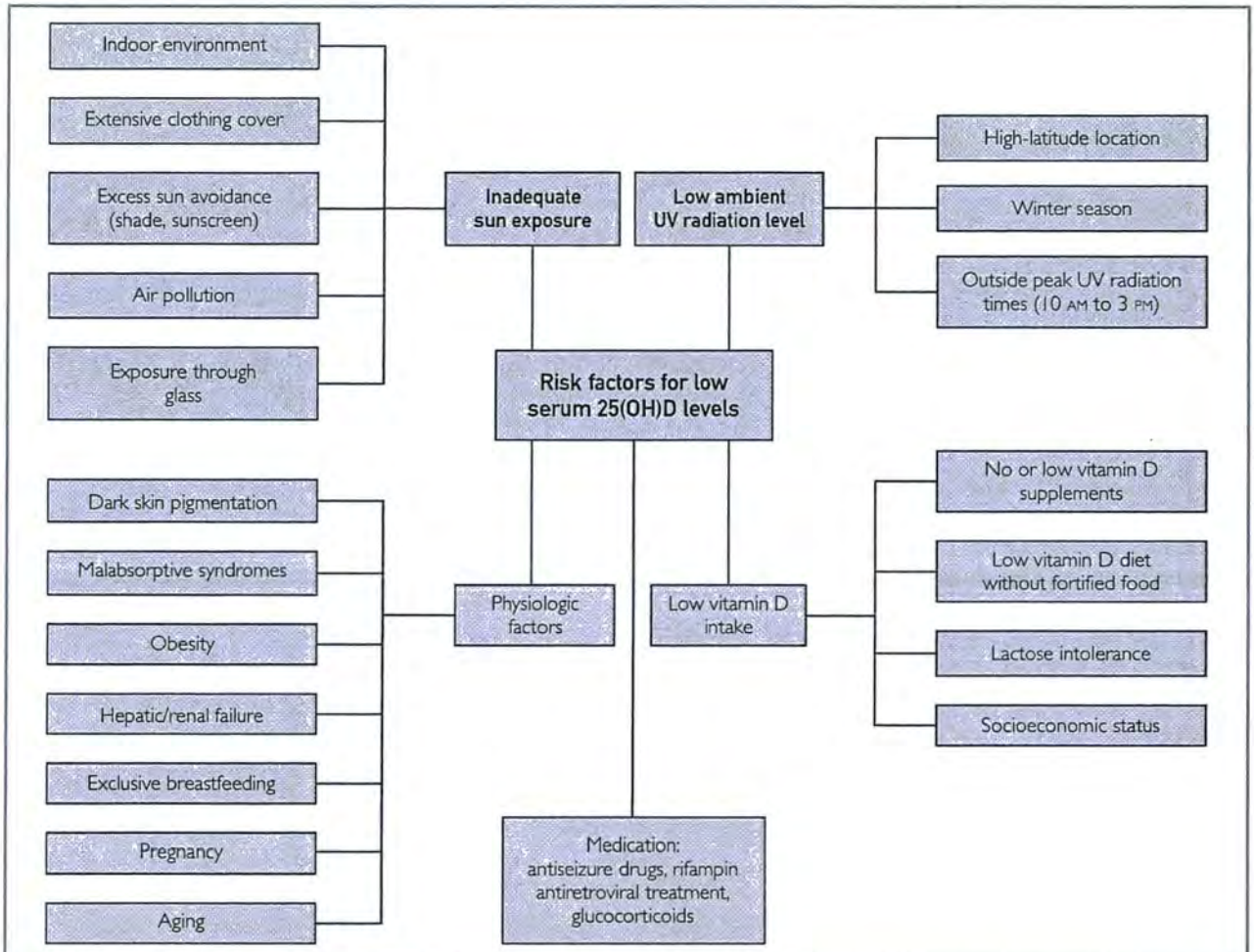

FIGURE 6. Risk factors for low vitamin D status. 25(OH)D = 25-hydroxyvitamin D. Copyright Holick 2013, reproduced with permission.

Although the heritability of vitamin D status seems considerable, the specific genetic determinants of 25(OH)D levels are only beginning to be identified. A recent examination of 141 single nucleotide polymorphisms (SNPs) in a discovery cohort of 1514 white participants from the community-based Cardiovascular Health Study found that lower serum 25(OH)D levels were associated with HRs for the risk of the composite outcome of 1.40 for those who had 1 minor allele at rs7968585 (in VDR) and 1.82 for those with 2 minor alleles.[238,239] This candidate gene study indicates that known associations of low serum 25(OH)D levels with clinical outcomes may vary according to genetic differences in the VDR. In black patients, there were significant associations in 3 SNPs in vitamin D pathway genes (rs2282679, rs2298849, and rs10877012), all of which replicate earlier findings in populations of European ancestry.[239] Included among these was rs2282679, a highly significant result from 2 recent genome-wide association studies (GWASs),[240,241] one of which reported a 49% increased risk of vitamin D deficiency (25[OH]D <20 ng/mL) associated with the rs2282679 minor allele in white individuals.[241] Another study of genetic predictors of 25(OH)D in black individuals involved 513 participants from 42 families in Los Angeles, California, and evaluated 30 SNPs in DBP, VDR, and CYP27B1.[242] Recent epigenomic findings confirmed 3 genes (*DHCR7*,

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CYP2R1, and *CYP24A1*) of the 4 genes in the GWAS findings, which reinforces the crucial roles played by those 3 genes in vitamin D metabolism.[243] *DHCR7* encodes the enzyme 7-DHC reductase, which converts 7-DHC to cholesterol, thereby removing the substrate from the synthetic pathway of vitamin D_3.[239] *DHCR7* is a novel gene for association with 25(OH)D levels, as identified in 2 recent GWASs.[240,241] *CYP24A1*, which encodes 25(OH)D–24-hydroxylase, has been identified as a candidate gene for vitamin D insufficiency in one GWAS but not in the other.[240-242] This mitochondrial protein initiates the degradation of $1,25(OH)_2D_3$ and plays a role in calcium homeostasis and vitamin D metabolism. These epigenomic findings suggest that individuals with vitamin D deficiency are more likely to have reduced synthesis and increased catabolism of 25(OH)D and $1,25(OH)_2D$.[243]

The genetic contributions to circulating 25(OH)D represent a complex trait for which family studies have estimated heritability ranging from 43% to 80%.[244] Genomic and epigenomic data integration provided greater understanding of the physiology and etiology of the complex traits. Further elucidation of the genetic architecture of this complex trait beyond environmental determinants of 25(OH)D has the potential to identify those at risk for vitamin D insufficiency.[244] It may also provide a useful proxy for lifetime vitamin D exposure that may be applied in instrumental variable analyses investigating the association between vitamin D and common complex diseases. However, a recent GWAS of prospectively collected 25(OH)D data in 5 studies with 5575 individuals reported that known GWAS-associated SNPs explain only a fraction of the observed variance in circulating 25(OH)D levels (ie, approximately 5.2%).[244] On rare occasions, some patients who deny taking a vitamin D supplement have unexplained high normal 25(OH)D levels in the range of 40 to 80 ng/mL. It is believed that this is due to a genetic mutation of the cyp24A1 that reduces the catabolism of 25(OH)D and $1,25(OH)_2D$ and can be a cause of infantile hypercalcemia.[245] Therefore, these recent genomic and epigenetic data provide additional evidence of genetic-environmental interactions and their effects on circulating 25(OH)D levels.

TREATMENT AND PREVENTION OF VITAMIN D DEFICIENCY AND INSUFFICIENCY WITH SUN EXPOSURE AND UV-B IRRADIATION

Humans obtain a considerable amount of their vitamin D requirement from sun exposure.[7,140] Although excessive exposure to sunlight increases the risk of nonmelanoma skin cancer, which is easy to detect and easy to treat, there is no evidence that sensible sun exposure, as our hunter-gatherer forefathers likely experienced, increases risk.[124,246] More importantly, the most deadly form of melanoma skin cancer that occurs on the least sun-exposed areas is less likely to occur in adults who have outdoor occupations.[1,124,246,247] Therefore, it is not unreasonable to consider sensible sun exposure as a good source of vitamin D.[7,124] An adult in a bathing suit exposed to 1 minimal erythemal dose (slight pinkness to the skin 24 hours after exposure) is the equivalent to taking approximately 20,000 IU (500 μg) of vitamin D_2 orally.[7,15] Thus, exposure of arms and legs to 0.5 minimal erythemal dose is equivalent to ingesting approximately 3000 IU of vitamin D_3.[7,60] Adults who frequented a tanning salon had robust levels of 25(OH)D, on average 46 ng/mL, and had higher bone mineral density in their hips compared with healthy adults who did not go to a tanning salon in Boston, Massachusetts, at the end of winter.[248] It was estimated that if all the people in the United States were to double their solar UV-B irradiance to raise their serum 25(OH)D levels to 45 ng/mL, the net result could be as many as 400,000 reduced deaths compared with only 11,000 increased deaths from melanoma and other skin cancer.[249] Time of day during sun exposure, season, latitude, and degree of skin pigmentation dictate how much vitamin D_3 is produced during sun exposure. Exposure of the arms and legs (abdomen and back when possible) to sunlight 2 to 3 times a week for approximately 25% to 50% of the time it would take to develop a mild sunburn (minimal erythemal dose) will cause the skin to produce enough vitamin D. For a white person, if 30 minutes of June noontime sun would cause a mild sunburn, then 10 to 15 minutes of exposure followed by good sun protection should be sufficient to produce adequate vitamin D.[7] There is no need to ever expose the face because although it is the most sun exposed of all the body areas, it provides little vitamin D_3. A free app, dminder.info, provides the user with

information about sensible sun exposure and vitamin D production. For patients with fat malabsorption syndromes that render oral consumption of supplemental vitamin D ineffective, exposure to a lamp that emits UV-B radiation can be effective in raising blood levels of 25(OH)D.[250]

Food Sources

Very few foods naturally contain vitamin D; examples of foods with ample vitamin D stores include wild-caught salmon and UV-exposed mushrooms.[7] Foods fortified with vitamin D usually contain 100 IU per serving. An analysis of the vitamin D intake of children and adults in the United States revealed that they were unable to achieve the RDA for vitamin D from any dietary sources.[251]

Vitamin D intake can be increased by eating foods fortified with vitamin D. A recent systematic review found that food fortification with vitamin D (especially in milk) is effective in significantly increasing 25(OH)D levels in the population.[7,252] Other foods include some cereals, juices, other dairy products, and some margarines. A mean individual intake of approximately 11 μg/d (440 IU/d) from fortified foods (range, 120-1000 IU/d) increased 25(OH)D concentrations by 7.7 ng/mL, corresponding to a 0.48-ng/mL increase in 25(OH)D for each 40 IU (1 μg) ingested.[252]

Vitamin D Supplementation

The RDA for vitamin D and tolerable upper-limit levels vary in different age groups and in certain circumstances.[7,60,62] Although it is recommended that RDAs of 600 to 800 IU daily should meet the requirements to optimize bone health[62] in most of the population, higher vitamin D intakes (1000-2000 IU) are needed to reach and maintain 25(OH)D levels greater than 30 ng/mL.[7,60] It is recognized that for every 100 IU of vitamin D ingested, the blood level of 25(OH)D increases by approximately 0.6 to 1 ng/mL.[253] When the serum 25(OH)D level is less than 15 ng/mL, 100 IU of vitamin D will increase the 25(OH)D level by as much as 2 to 3 ng/mL.[7,71] An effective strategy to treat vitamin D deficiency and insufficiency in children and adults is to give them 50,000 IU of vitamin D_2 once a week for 6 and 8 weeks, respectively.[60,254] To prevent recurrence of vitamin D deficiency in children, administration of 600 to 1000 IU/d is effective.[60] For adults, to prevent recurrence of vitamin D deficiency, administration of 50,000 IU of vitamin D_2 every 2 weeks is effective.[7,60,255] This strategy was shown to be effective in maintaining blood levels of 25(OH)D at approximately 40 to 60 ng/mL for up to 6 years without any evidence of toxic effects.[255]

Vitamin D can be administered daily, weekly, monthly, or every 4 months to sustain an adequate serum 25(OH)D concentration.[7,256-258] A bolus of high doses of vitamin D (up to 300,000 IU) can be initially used in persons with extreme vitamin D deficiency. Repeated boluses of high-dose vitamin D at 6- to 12-month intervals have been used in a nursing home setting, but a steady-state serum 25(OH)D concentration is likely to be maintained by more frequent, lower doses of vitamin D. One study has suggested that a 500,000-IU bolus dose of vitamin D_3 increases the risk of fracture within 3 months,[256] but other studies have reported reduced risk of fracture.[257,258]

Vitamin D Supplementation During Pregnancy and Lactation

The 25(OH)D passes from the placenta into the bloodstream of the fetus. Because the half-life for 25(OH)D is approximately 2 to 3 weeks, the infant can remain vitamin D sufficient for several weeks after birth, as long as the mother is vitamin D sufficient.[2]

In a study of 40 mostly black pregnant women who were documented to be ingesting approximately 600 IU of vitamin D a day, at the time that they gave birth, 76% were vitamin D deficient as defined by the IOM cutoff value of a 25(OH)D level less than 20 ng/mL.[259] Eighty-one percent of their newborns were vitamin D deficient.[259] Maternal supplementation with 2000 and 4000 IU/d of vitamin D during pregnancy improved the maternal/neonatal vitamin D status.[260] None of the pregnant women developed significant changes in their serum calcium or 24-hour urinary calcium levels. Evidence of risk reduction in infection, preterm labor, and preterm birth was suggestive, requiring additional studies powered for these end points.[260,261]

Human breast milk and unfortified cow's milk have little vitamin D.[7,260,261] Only after lactating women were given 4000 to 6000 IU/d of vitamin D was enough vitamin D transferred in breast milk to satisfy the infant's requirement.[260,261]

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Vitamin D Supplementation in Special Conditions

Because body fat can sequester vitamin D, it is now recognized that children and adults who are obese require 2 to 5 times more vitamin D to treat and prevent vitamin D deficiency.[7,60] Patients taking antiseizure medications, AIDS medications, and glucocorticoids often require more vitamin D to satisfy their requirements.[7,60] However, patients with granulomatous disorders, such as sarcoidosis and tuberculosis, are at risk for hypercalciuria and hypercalcemia when blood levels of 25(OH)D are greater than 30 ng/mL owing to the increased serum levels of $1,25(OH)_2D$ produced in the macrophages in the granulomas.[7] Therefore, their vitamin D intake needs to be carefully monitored and controlled.[7,60] Hence, daily requirements of vitamin D to reach and maintain the desired serum 25(OH)D level can be estimated from the baseline 25(OH)D concentration. Supplemental vitamin D is preferentially administered orally or intramuscularly (not available in the United States), and the vitamin D–producing Sperti lamp can be used, where available, in patients with malabsorption syndromes.[250,262]

Type of Vitamin D Supplementation

Either vitamin D_2 or vitamin D_3 can be used for vitamin D supplementation, although there is controversy regarding vitamin D_3 vs vitamin D_2 for achieving and maintaining higher serum 25(OH)D levels. Although a recent meta-analysis indicated that vitamin D_3 is more efficacious at raising serum 25(OH)D concentrations than is vitamin D_2,[2,102] several prospective studies have found them to be equally effective in raising and maintaining serum 25(OH)D levels in children and adults.[263,264] Holick et al[264] found that an 11-week course of treatment with 1000 IU/d of vitamin D_2, 1000 IU/d of vitamin D_3, or a combination of 500 IU of vitamin D_2 and 500 IU of vitamin D_3 daily caused an equivalent increase in serum total 25(OH)D levels. Furthermore, the group that received vitamin D_2 did not experience a significant change in serum $25(OH)D_3$ levels. Gordon et al[265] and Thacher et al[266] also found that in infants and toddlers treated for 6 weeks, 2000 IU of vitamin D_2 and 2000 IU of vitamin D_3 daily or a single dose of 50,000 IU of vitamin D_2 or vitamin D_3 were equally effective in increasing the serum total 25(OH)D level. The bioavailability of vitamin D_3 is well established, and the bioavailability of vitamin D_2 from mushrooms in humans has been found to be comparable with that of a vitamin D_2 supplement.[267] Finally, adults treated with vitamin D_2 not only raised their total blood levels of 25(OH)D but also maintained total blood levels of $1,25(OH)_2D$ to the same degree as adults who received the same dose of vitamin D_3.[263]

SAFETY AND INTOXICATION

Vitamin D intoxication is characterized by hypercalcemia, hypercalciuria, and hyperphosphatemia, which, in turn, are responsible for soft-tissue and vascular calcifications and nephrolithiasis in the long term. Serum 25(OH)D levels are usually markedly elevated (>150 ng/mL) in individuals with vitamin D intoxication.[7,60,90] Daily doses of vitamin D_3 up to 10,000 IU were safe in healthy males, and there was no evidence of hypercalcemia or hypercalciuria for 5 months.[253,268] This amount is far above the tolerable upper level indicated in the IOM guidelines (4000 IU). Higher doses of vitamin D (up to 40,000 IU/d) are still safe provided that a serum 25(OH)D concentration of 200 ng/mL is not exceeded. A recent report of an infant inadvertently receiving 12,000 IU of vitamin D_3 daily for 20 days and achieving a serum 25(OH)D level of 425 ng/mL had no signs of vitamin D intoxication. Once the vitamin D use was stopped, the serum 25(OH)D level was less than 100 ng/mL within 2 months.[269]

CONCLUSION

Vitamin D deficiency is a common underdiagnosed condition that has received increasing attention in the world. The US Endocrine Society guidelines and the IOM recommend screening only in populations at risk, as no evidence currently exists to support screening at a population level. Candidates for vitamin D screening include those who are at specific risk for vitamin D deficiency and patients who are experiencing or are at risk for specific medical conditions associated with hypovitaminosis D.

Recent evidence from hundreds of studies has suggested that vitamin D is important for reducing the risk of a variety of chronic illnesses. The identification of a VDR in most tissues and cells and the observation that a multitude of genes may be directly or indirectly regulated by $1,25(OH)_2D$ have provided a

rationale for the nonskeletal health benefits of vitamin D. A study in healthy adults who received either 400 or 2000 IU/d of vitamin D_3 for 3 months in winter reported that 291 genes were either up-regulated or down-regulated. That these genes affected as many as 80 different metabolic pathways (from immune modulation to enhanced antioxidant activity) emphasizes the importance of improving the world's vitamin D status.[17] The observation that $1,25(OH)_2D$ may also influence epigenetics provides additional support for the concept that there is no downside to increasing the vitamin D status of children and adults. Vitamin D deficiency during pregnancy may adversely influence placental development and fetal programming. Vitamin D deficiency in both parents may influence adverse pregnancy outcomes and susceptibility to developing disease in adult life and even into the next generation.

There is potentially a great upside (in terms of improving overall health and well-being) to increasing serum 25(OH)D levels above 30 ng/mL. An effective strategy to prevent vitamin D deficiency and insufficiency is to obtain some sensible sun exposure, ingest foods that contain vitamin D, and take a vitamin D supplement.

Abbreviations and Acronyms: **CD** = Crohn disease; **DBP** = vitamin D binding protein; **DC** = dendritic cell; **ESCEO** = European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis; **GWAS** = genome-wide association study; **HR** = hazard ratio; **ILT** = immunoglobulin-like transcript; **IOM** = Institute of Medicine; **IVF** = in vitro fertilization; **LC-MS/MS** = liquid chromatography–tandem mass spectrometry; **LPS** = lipopolysaccharide; **miRNA** = microRNA; **MS** = multiple sclerosis; **NHANES** = National Health and Nutrition Examination Survey; **OR** = odds ratio; **PTH** = parathyroid hormone; **PTHrP** = parathyroid hormone–related protein; **RA** = rheumatoid arthritis; **RDA** = recommended dietary allowance; **RCT** = randomized controlled trial; **RR** = risk rate; **SE** = standard error; **SNP** = single nucleotide polymorphism; **T_H** = T helper cell; **VDR** = vitamin D receptor; **WHI** = Women's Health Initiative; **$1,25(OH)_2D$** = 1α,25-dihydroxyvitamin D; **7-DHC** = 7-dehydrocholesterol; **25(OH)D** = 25-hydroxyvitamin D

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