

**HB**

**39**

<TARGET><BILL>HB 39</BILL><SUBJECT>HB  
39</SUBJECT><COMM>HHSS29</COMM></TARGET>

29-LS0227\W  
Wayne  
2/4/15

**CS FOR HOUSE BILL NO. 39( )**  
**IN THE LEGISLATURE OF THE STATE OF ALASKA**  
**TWENTY-NINTH LEGISLATURE - FIRST SESSION**

**BY**

**Offered:**  
**Referred:**

**Sponsor(s): REPRESENTATIVES SEATON, Millett, Vazquez**

**A BILL**  
**FOR AN ACT ENTITLED**

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

3 **BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF ALASKA:**

4 **\* Section 1.** The uncodified law of the State of Alaska is amended by adding a new section  
5 to read:

6 **LEGISLATIVE FINDINGS AND INTENT.** (a) The legislature finds that

7 (1) individual Alaskans and the state share the burden of increasing health care  
8 and insurance costs resulting from avoidable disease in humans;

9 (2) state policy should focus more on avoiding disease and maintaining good  
10 health in the state's population;

11 (3) the state relies partly on federal one-size-fits-all human health policy  
12 recommendations, creating federal overreach into the state's administration of health policy;

13 (4) the state's human health policies should incorporate peer-reviewed  
14 scientific studies that illustrate health-related differences between the population of the state

1 and the populations of other states;

2 (5) the health policies of the state can affect the frequency and severity of  
3 disease present in the state's population;

4 (6) by establishing wellness initiatives to decrease the frequency and severity  
5 of disease present in the state's population, the state can slow the rate of annual growth in the  
6 state's cost of providing health care benefits to persons who are covered by a policy of group  
7 health insurance obtained under AS 39.30.090(a) or 39.30.091(a).

8 (b) It is the intent of the legislature that, by establishing a wellness committee and  
9 wellness initiatives that create incentives and methods to decrease the frequency and severity  
10 of disease in the state's population, the state will slow the rate of growth in the state's cost of  
11 providing health care benefits to persons who are covered by a policy of group health  
12 insurance obtained under AS 39.30.090(a) or 39.30.091(a) to a rate that does not exceed two  
13 percent annually.

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

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

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

23 (b) To the greatest extent legally and reasonably practicable, the Department  
24 of Administration shall work to hold the escalation of health care costs to less than two  
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26 this section in a manner that is likely to reduce the incidence of disease in the state's  
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28 Advisory Committee on Wellness established under AS 39.30.093.

29 \* **Sec. 4.** AS 39.30 is amended by adding a new section to read:

30 **Sec. 39.30.093. Advisory Committee on Wellness.** (a) The Advisory  
31 Committee on Wellness is established in the Department of Administration. The

1 committee consists of at least seven volunteer members appointed by the  
2 commissioner of administration who serve at the pleasure of the commissioner.

3 (b) The committee shall select one of its members as chair.

4 (c) The commissioner shall appoint members who represent each region of the  
5 state to give the committee a reasonable geographic balance among regions of the state  
6 and shall appoint at least one member who is a professional provider of medical  
7 services.

8 (d) The committee shall meet at the call of the chair or at the request of a  
9 majority of its members. A member may attend a meeting by telephone or other means  
10 of telecommunication.

11 (e) At intervals of six months, the committee shall make recommendations to  
12 the commissioner of administration regarding the adoption of wellness initiatives to  
13 improve the physical and mental health of persons who are covered by a policy of  
14 group health insurance obtained under AS 39.30.090(a) or 39.30.091(a).

15 (f) Not later than six months after receiving a recommendation made under (e)  
16 of this section, the commissioner of administration shall provide to the committee a  
17 report on the commissioner's progress in advancing the recommendation and the  
18 recommendation's effect on

19 (1) the health of the population covered by a policy of group health  
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21 (2) the state's cost of providing health care to persons who are covered  
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23 (g) On or before the second Monday in December of each year, the  
24 commissioner of administration shall deliver to the governor, the senate secretary, and  
25 the chief clerk of the house of representatives a copy of reports the commissioner has  
26 made in the preceding 12-month period under (f) of this section and notify the  
27 legislature that the reports are available.

28 (h) On or before the second Monday in December of each year, the committee  
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30 representatives a written report containing the recommendations the committee has  
31 made in the preceding 12-month period under (e) of this section and notify the

1 legislature that the report is available.

2 (i) Members of the committee serve without compensation.

**HOUSE BILL NO. 39**

IN THE LEGISLATURE OF THE STATE OF ALASKA

TWENTY-NINTH LEGISLATURE - FIRST SESSION

BY REPRESENTATIVE SEATON

Introduced: 1/9/15

Referred: Prefiled

**A BILL**

**FOR AN ACT ENTITLED**

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21 (2) the state's cost of providing health care to persons who are covered  
22 by a policy of group health insurance obtained under AS 39.30.090(a) or 39.30.091(a).

23 (g) Members of the committee serve without compensation.

AMENDMENT

OFFERED IN THE HOUSE

TO: HB 39

1 Page 3, following line 22:

2 Insert new subsections to read:

3 "(g) On or before the second Monday in December of each year, the  
4 commissioner of administration shall deliver to the governor, the senate secretary, and  
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12 legislature that the report is available."

13

14 Reletter the following subsection accordingly.

# Alaska State Legislature

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

## **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 \$400 million. 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 treatment of 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.

# Alaska State Legislature

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

### 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 legal 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 legal 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.

# Fiscal Note

State of Alaska  
2015 Legislative Session

Bill Version: HB 39  
Fiscal Note Number: \_\_\_\_\_  
( ) Publish Date: \_\_\_\_\_

Identifier: HB039-DOA-DRB-01-21-15  
Title: PUBL EMPL HEALTH INS; WELLNESS  
COMMITTEE  
Sponsor: SEATON  
Requester: House Health and Social Services

Department: Department of Administration  
Appropriation: Centralized Administrative Services  
Allocation: Retirement and Benefits  
OMB Component Number: 64

**Expenditures/Revenues**

Note: Amounts do not include inflation unless otherwise noted below. (Thousands of Dollars)

	FY2016 Appropriation Requested	Included in Governor's FY2016 Request	Out-Year Cost Estimates					
			FY 2016	FY 2017	FY 2018	FY 2019	FY 2020	FY 2021
<b>OPERATING EXPENDITURES</b>								
Personal Services								
Travel								
Services								
Commodities								
Capital Outlay								
Grants & Benefits								
Miscellaneous								
<b>Total Operating</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

**Fund Source (Operating Only)**

None								
<b>Total</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

**Positions**

Full-time								
Part-time								
Temporary								

<b>Change in Revenues</b>								
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**Estimated SUPPLEMENTAL (FY2015) cost:** 0.0 *(separate supplemental appropriation required)*  
*(discuss reasons and fund source(s) in analysis section)*

**Estimated CAPITAL (FY2016) cost:** 0.0 *(separate capital appropriation required)*  
*(discuss reasons and fund source(s) in analysis section)*

**ASSOCIATED REGULATIONS**

Does the bill direct, or will the bill result in, regulation changes adopted by your agency? No  
If yes, by what date are the regulations to be adopted, amended or repealed? N/A

**Why this fiscal note differs from previous version:**

Not applicable, initial version.

Prepared By:	Michele Michaud, Chief Health Official	Phone:	(907)465-3225
Division:	Division of Retirement and Benefits	Date:	01/21/2015 12:00 AM
Approved By:	Sheldon Fisher, Commissioner	Date:	01/23/15
Agency:	Department of Administration		

FISCAL NOTE ANALYSIS

STATE OF ALASKA  
2015 LEGISLATIVE SESSION

BILL NO. HB 39

**Analysis**

HB 39 establishes an advisory committee on wellness in the Department of Administration and requires the Department to focus on wellness in an effort to limit the annual increase in health care costs for State of Alaska Employees/Dependents covered under AlaskaCare, Participating Political Subdivision Employees/Dependents, and AlaskaCare Retirees/Dependents to less than 2%.

The wellness committee would consist of at least seven volunteer members appointed by the Commissioner of the Department of Administration. The committee would make recommendations to the Commissioner of Administration regarding to adoption of wellness initiatives to improve the health of State of Alaska Employees/Dependents covered under AlaskaCare, Participating Political Subdivision Employees/Dependents, and AlaskaCare Retirees/Dependents.

HB 39 also requires, to the extent legally and reasonably practicable, the Department of Administration shall work to hold the escalation of health care cost growth to less than 2% for health insurance plans administered or purchased by the Department.

The costs associated with the creation of the committee and coordinating committee meetings would be minimal and absorbed in the cost of normal business for the Department. The costs of specific initiatives recommended by the advisory committee on wellness, some of which could be substantial, cannot be estimated at this time. Therefore, the Department submits a zero fiscal note.

# ALASKA HEALTHCARE COSTS

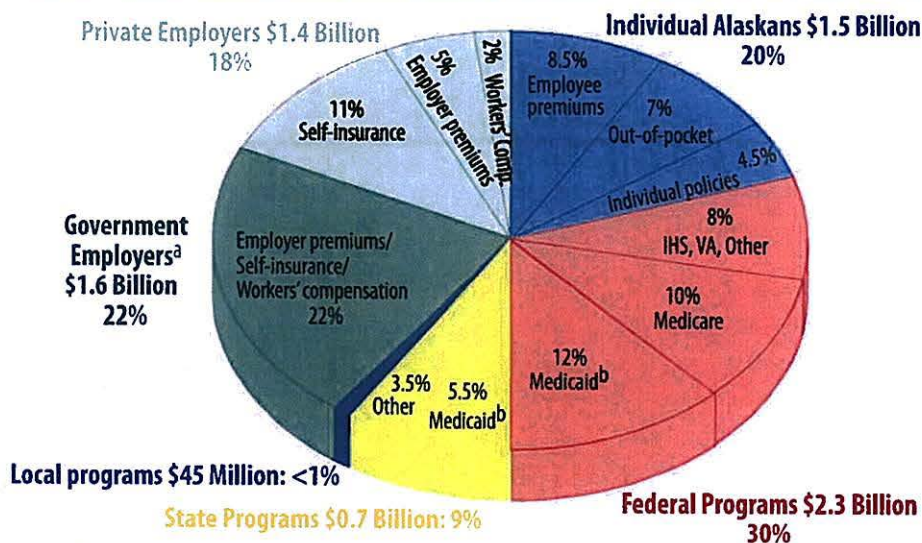
# Alaska's Health-Care Bill: \$7.5 Billion and Climbing

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)



<sup>a</sup>Insufficient data to break out categories

<sup>b</sup>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.

### What Do Health-Care Dollars Buy?

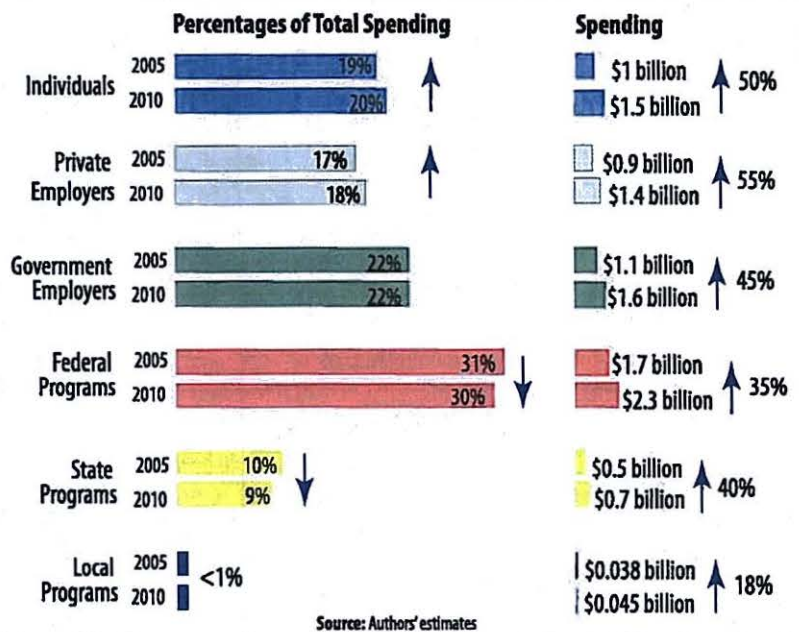
Alaska's \$7.5 billion health-care bill includes everything from visits to doctors and dentists to prescriptions and nursing-home care.<sup>5</sup> Figure 7 summarizes what Alaska's health-care dollars bought in 2010.

- *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.*

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



### How About Health-Care Jobs?

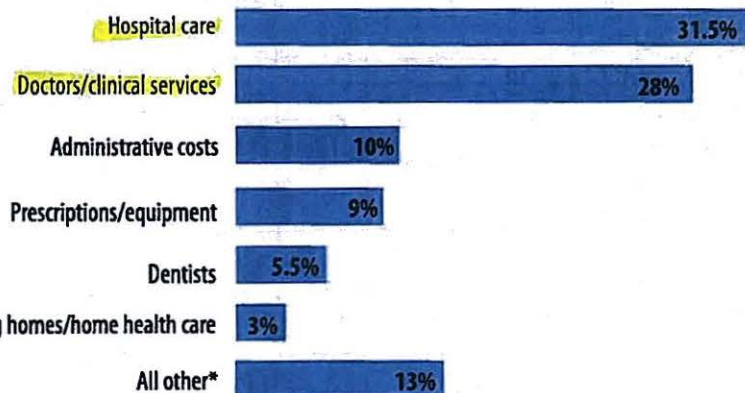
This summary looks at health care from the perspective of spending for care—but it's important to remember that the spending also supports jobs for Alaskans. As the Alaska Department of Labor and Workforce Development reports in its August 2011 *Alaska Economic Trends*:

- *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)

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

4th Quarter Report 2013

ACTIVE PLAN

**Aggregate Risk Profile**

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

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

## RETIREE PLAN



### 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%

AlaskaCare Retiree Plan - 4th Quarter Report 2013

Notes in red by office of Rep. Seaton

## **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.

Employee health status significantly impacts workplace productivity and overall business performance.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup> Presenteeism, not absenteeism or disability, accounts for the majority of lost productive time due to both pain conditions<sup>4</sup> and depression.<sup>5</sup> Surprisingly, for 18 common health conditions, presenteeism alone contributes 14% to 73% to total employer health care costs.<sup>3</sup> Presenteeism may cost US employers more than \$150 billion per year.<sup>6</sup>

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.<sup>7</sup> 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,<sup>8</sup> including chronic

## 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.

nonspecific musculoskeletal pain,<sup>9,10</sup> low back pain,<sup>11-13</sup> allergic rhinitis,<sup>14</sup> arthritis,<sup>15-18</sup> asthma,<sup>19-21</sup> cancer,<sup>22-26</sup> depression,<sup>27-30</sup> diabetes,<sup>31,32</sup> gestational diabetes,<sup>33</sup> heart disease,<sup>34,35</sup> hypertension,<sup>36,37</sup> migraine/headache,<sup>38</sup> and respiratory disorders.<sup>39-42</sup> Additional associations related to impaired productivity may include impaired cognition,<sup>43,44</sup> falls,<sup>45</sup> and bone fractures.<sup>46</sup> 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<sup>47</sup> 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.<sup>47</sup>

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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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**

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

**= \$112 Per Employee Per Year or  
total of \$2.3 Million Per Year**

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

**= \$370 Per Employee Per Year or  
total of \$7.7 Million Per Year**

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

## 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

William B. Grant<sup>1</sup>, Cedric F. Garland<sup>2</sup> and Michael F. Holick<sup>3</sup>

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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)<sub>2</sub>D<sub>3</sub>, 1,25-dihydroxy vitamin D<sub>3</sub>; 25(OH)D, 25-hydroxyvitamin D.

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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**

## 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.

Received: October 10, 2009  
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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.

## 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 three times 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

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**Abbreviation:** RCT, randomized controlled trial

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



# LEGISLATIVE RESEARCH SERVICES

Alaska State Legislature  
Division of Legal and Research Services  
State Capitol, Juneau, AK 99801

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## Research Brief

TO: Representative Paul Seaton  
FROM: Tim Spengler, Legislative Analyst  
DATE: February 28, 2014  
RE: Average Annual Cost Estimates Related to Diabetes and Cancer  
*LRS Report 14.251*

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*You asked for estimates on the average annual medical costs for individuals with diabetes and cancer. You requested estimates that consider a number of factors including doctor visits, equipment, and expected procedures, if available.<sup>1</sup>*

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### **Diabetes Cost Estimates**

According to a major research study released in March 2013 commissioned by the American Diabetes Association (ADA), the estimated total costs of diagnosed diabetes nationwide have risen by 41 percent from 2007 to 2012.<sup>2</sup> Nationwide, costs associated with diabetes have increased from \$174 to \$245 billion during this time period. Most of these costs pertain to medical expenses although a portion relates to reduced productivity of diagnosed individuals. This in-depth study addresses the increased financial burden, health resources used, and lost productivity associated with diabetes.<sup>3</sup>

As for **annual costs**, the study concludes that people with diagnosed diabetes incur average medical expenditures directly attributable to the condition of around **\$7,900**. The largest medical expenditures are

- hospital inpatient care (43 percent of total medical cost);
- prescription medications (18 percent);
- anti-diabetic agents and diabetic supplies (12 percent);
- physician office visits (9 percent); and
- nursing/residential facility stays (8 percent).

Indirect costs of the disease pertain to the reduced productivity of those with diabetes. Such costs include increased absenteeism, reduced productivity in the workplace, inability to work as a result of disease-related disability, and lost productive capacity due to early mortality. Such costs exist, but were not calculated on a per person average.

The ADA-commissioned study also relates that people with diagnosed diabetes, on the average, have medical expenditures approximately 2.3 times higher than what expenditures would be in the absence of diabetes. Additionally, more than one in ten health care dollars spent in the United States is spent directly on diabetes and its related complications.

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<sup>1</sup> You were also interested in the prevalence of diabetes and cancer among active and retired State of Alaska employees. We looked, but found no such data.

<sup>2</sup> You were particularly interested in costs for type 2 diabetes. While the study does not disaggregate by type, around 95 percent of diabetes cases are of the type 2 variety.

<sup>3</sup> The American Diabetes Association-commissioned study, "Economic Costs of Diabetes in the U.S. in 2012," can be accessed at <http://care.diabetesjournals.org/content/36/4/1033.full>.

According to the ADA, in 2012 there were around 22.3 million people—about seven percent of the U.S. population—with diagnosed diabetes. As many as seven million more people, by some estimates, likely have the disease but are, as of yet, unaware of it. Should current trends continue, by 2050, up to one in three American may have diabetes.

### ***Cancer Cost Estimates***

We identified the cancer cost estimates in this section from a 2013 study funded by the Centers for Disease Control (CDC) and published by American Cancer Society. The study's findings are presented in a June 2013 original article entitled "State-Level Cancer Treatment Costs," which we include as Attachment A.<sup>4</sup> According to the authors it is the first time state-level estimates of cancer treatment costs have been published.

The study, which looked at cancer care costs across the nation during 2004 to 2008, concludes that expenditures for cancer treatment were substantial in all states and accounted for a sizable fraction of medical expenditures for all payers: Medicare, Medicaid, and private insurance. The high financial costs that cancer imposes on society underscore the importance of preventing and controlling cancer as one approach to managing state-level costs, according to the article. This is in addition to, of course, the terrible human costs that the disease causes.

The estimated average annual cancer cost per person in Alaska during 2004 to 2008 was right around \$10,000 a year.<sup>5</sup> This is slightly less than the \$11,100 average for all states. Treatment costs were highest in Michigan at around \$12,600 per year, while Arizona and California were the least expensive at around \$9,600. The study did not disaggregate costs by particular types of cancer.<sup>6</sup> The article includes a great deal of additional information that you may find of interest. For example, Table 1 estimates the average annual cancer prevalence rates for each state. Alaska's rate for all residents was 3.3 percent compared to the median national average of 4.2 percent. \*

Another document that you may find illuminating is the American Cancer Society's "Cancer Facts and Figures, 2014." The document estimates that in 2014 about 1,665,540 new cancer cases are expected to be diagnosed across the country. Of these diagnoses, it is estimated that 3,750 will occur in Alaska.<sup>7</sup> It also disaggregates the estimated cancers by type; in Alaska, the most commonly diagnosed cancers are predicted to be prostate, breast, lung, and colon in that order.

Finally, you may wish to peruse the CDC's "Cancer Rates by States" (<http://www.cdc.gov/cancer/dcpc/data/state.htm>). The site includes both incident and death rates for cancer disaggregated by state and type of cancer. The prevalence rates in Alaska appear to be generally on the middle or lower end of the nationwide spectrum.

We hope this is helpful. If you have questions or need additional information, please let us know.

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<sup>4</sup> An "original" research article is a detailed account of research activity written by the scientists who did the research—not by someone else who is reporting on the research; it is considered a primary resource.

<sup>5</sup> Considering inflation, \$10,000 in 2008 would be equivalent to around \$11,000 in 2014. \*

<sup>6</sup> Another resource is the CDC's "cost calculator" for various chronic diseases, including cancer. The calculator must be downloaded but worked well for us. The calculator estimates the cost per person to treat cancer in Alaska to be nearly \$10,000, the same cost as "State-Level Cancer Treatment Costs," which the CDC was also involved with.

<sup>7</sup> This document can be accessed at <http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf>. Information on rates by state can be found on pages five through eight.

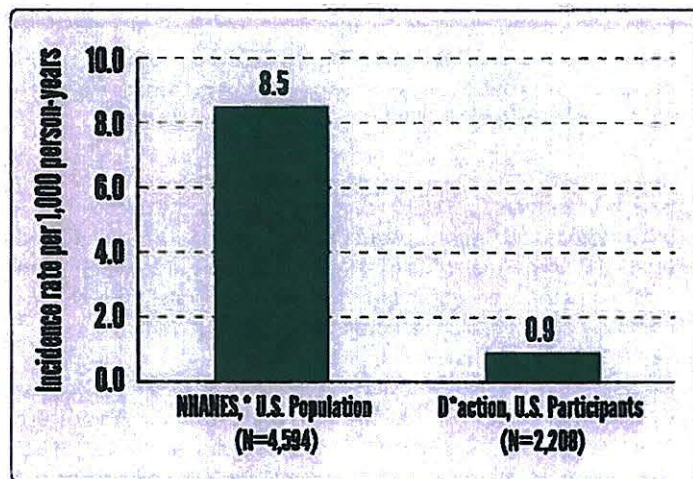
**Diabetes Incidence:  
Comparing NHANES and D\*action (18+ years)**

In a comparison of data from the National Health and Nutrition Examination Survey (NHANES), 2005-2006, and GrassrootsHealth D\*action participants in the United States, we found the following:

**Incidence of Diabetes:**

NHANES: 8.5/1,000 person-years  
D\*action: 0.9/1,000 person-years

A full 90% reduction in incidence - before adjusting for co-factors.



NHANES blood level 21 ng/ml

D\*Action blood level 48 ng/ml

(Both groups had a similar average BMI, within 3 points.)

Rate Ratio = 9.7 (P=0.0002)

Chart Date: 8/6/13

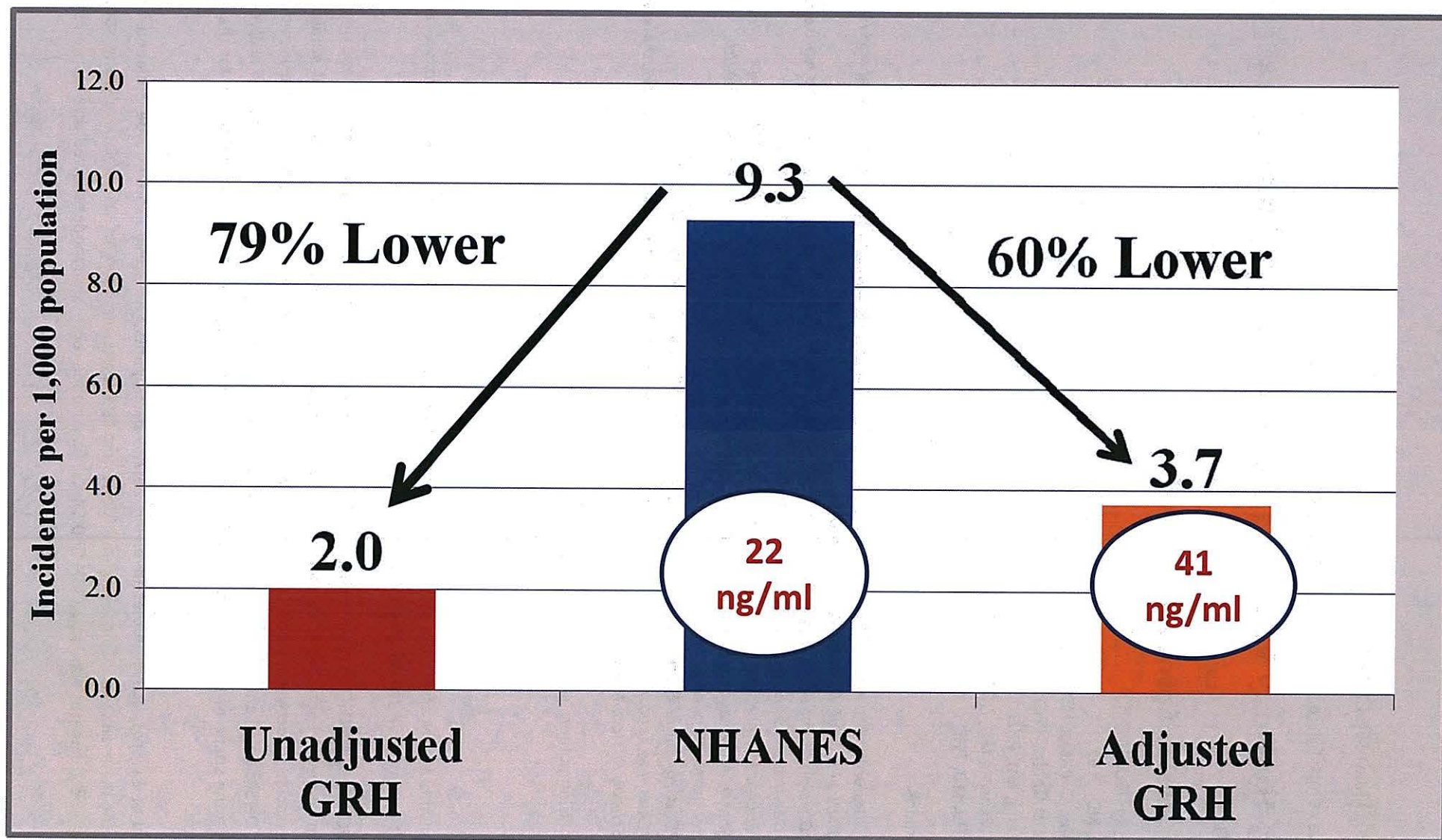
© 2013 GrassrootsHealth. Preliminary data, not yet published.



**GrassrootsHealth**  
A Public Health Promotion Organization

[www.grassrootshealth.net](http://www.grassrootshealth.net)

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



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

(Notes by Rep Seaton)

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

## A meta-analysis of prospective studies

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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

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

Yanlei Ma, Peng Zhang, Feng Wang, Jianjun Yang, Zhihua Liu, and Huanlong Qin

### A B S T R A C T

#### 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

All authors: The Sixth People's Hospital affiliated with Shanghai Jiao Tong University, Shanghai, People's Republic of China.

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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

### 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.<sup>1-2</sup> 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.<sup>3-6</sup> 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.<sup>7</sup> Therefore, low vitamin D levels may increase the risk of colorectal cancer through the above potential mechanism. Currently, vitamin D deficiency is an impor-

tant health problem in the industrial world<sup>8-9</sup>; in the United States, 25% to 58% of adolescents and adults are deficient in vitamin D.<sup>10</sup>

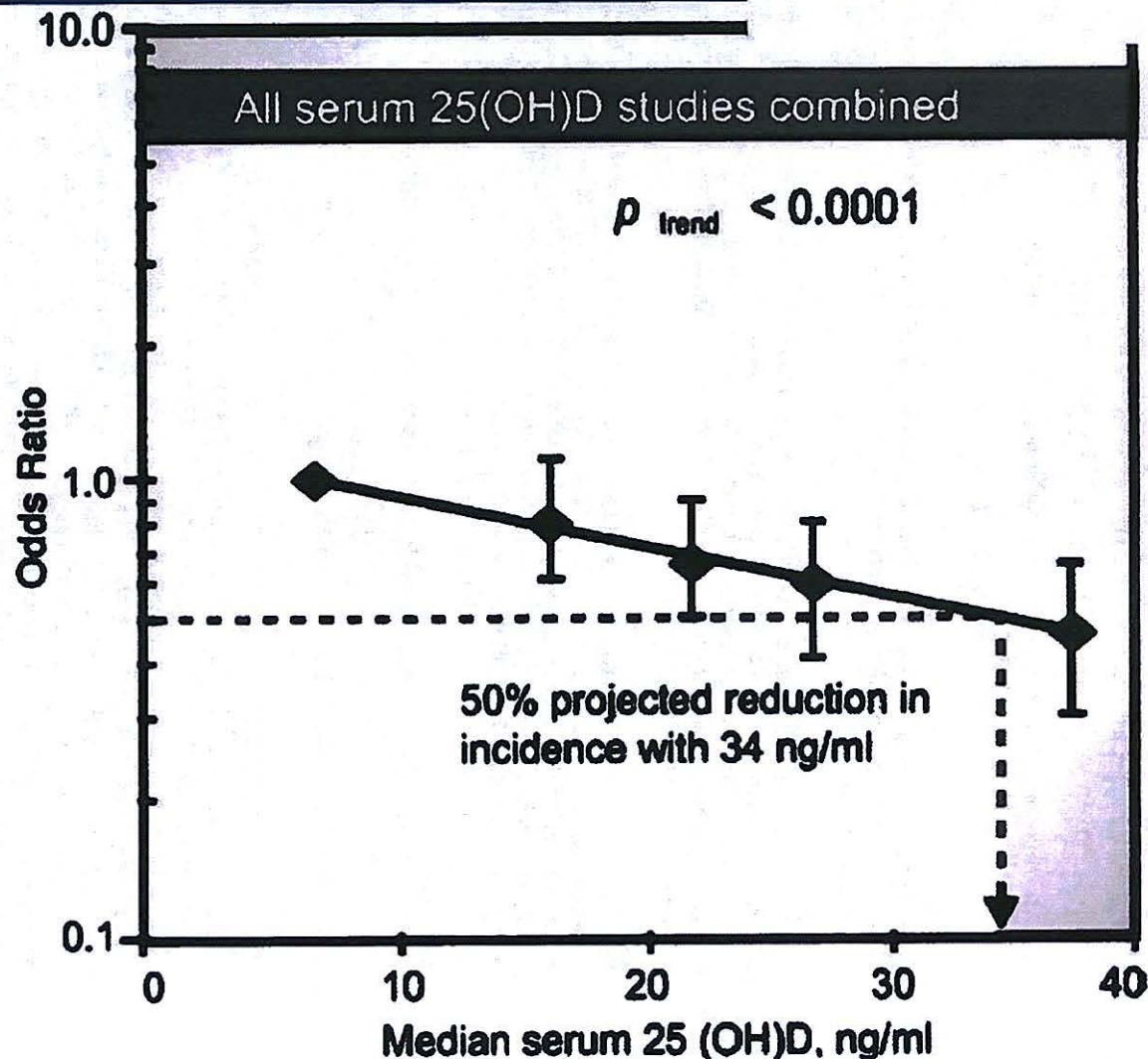
The results from prospective studies that have examined the association between vitamin D intake or 25(OH)D levels in the blood and the risk of colorectal cancer have been inconsistent. The aim of this review was to evaluate the evidence from prospective studies on vitamin D intake or blood levels of 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

# Meta-analysis



**Figure 1.** Dose-response gradient for colorectal cancer according to serum 25(OH)D concentration, all five studies combined.<sup>1,4-7</sup> 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**

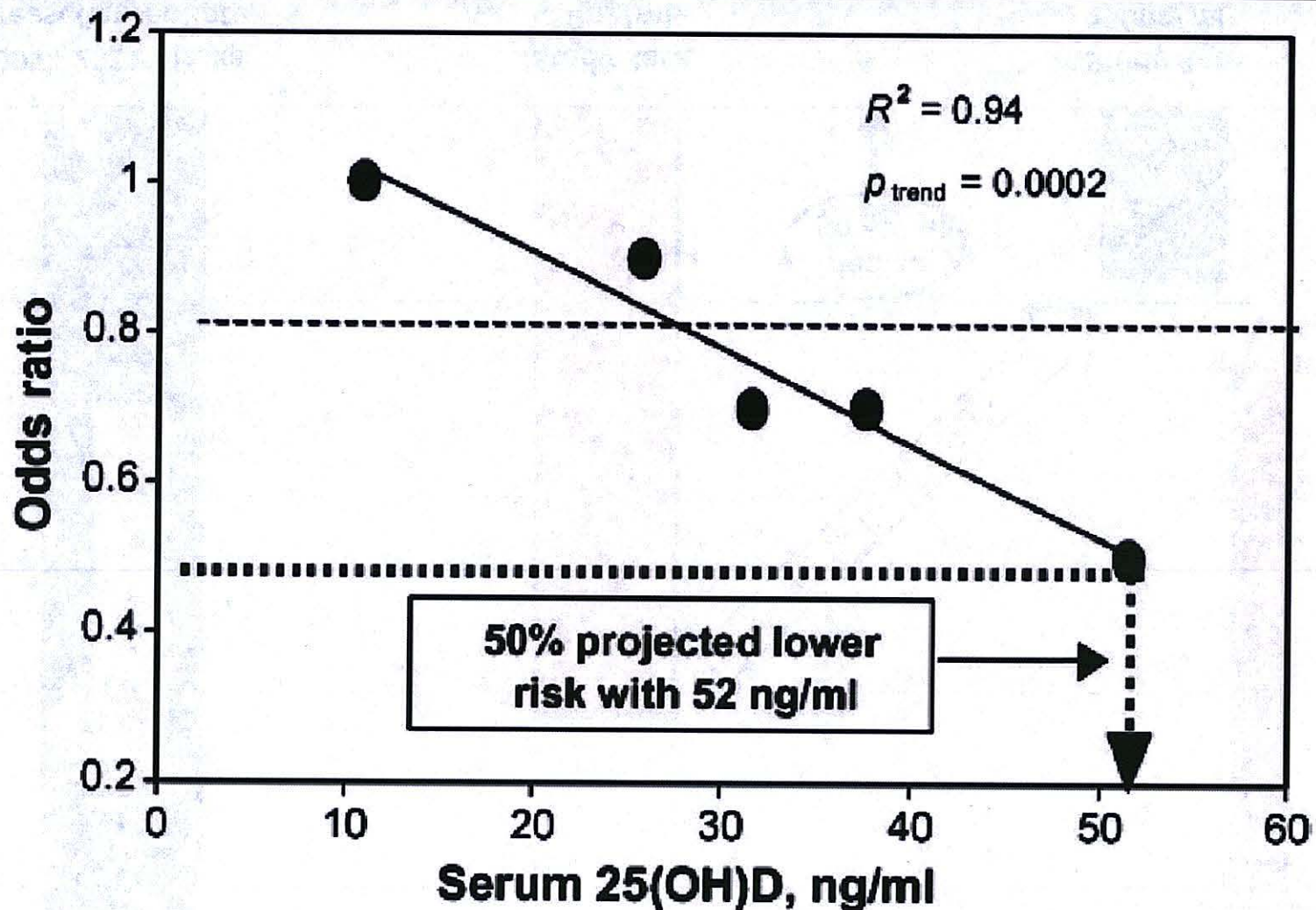
**\$1,962,950**

**(meta-analysis Gorham et. al.)**

# BREAST CANCER

# Meta-analysis of breast cancer risk

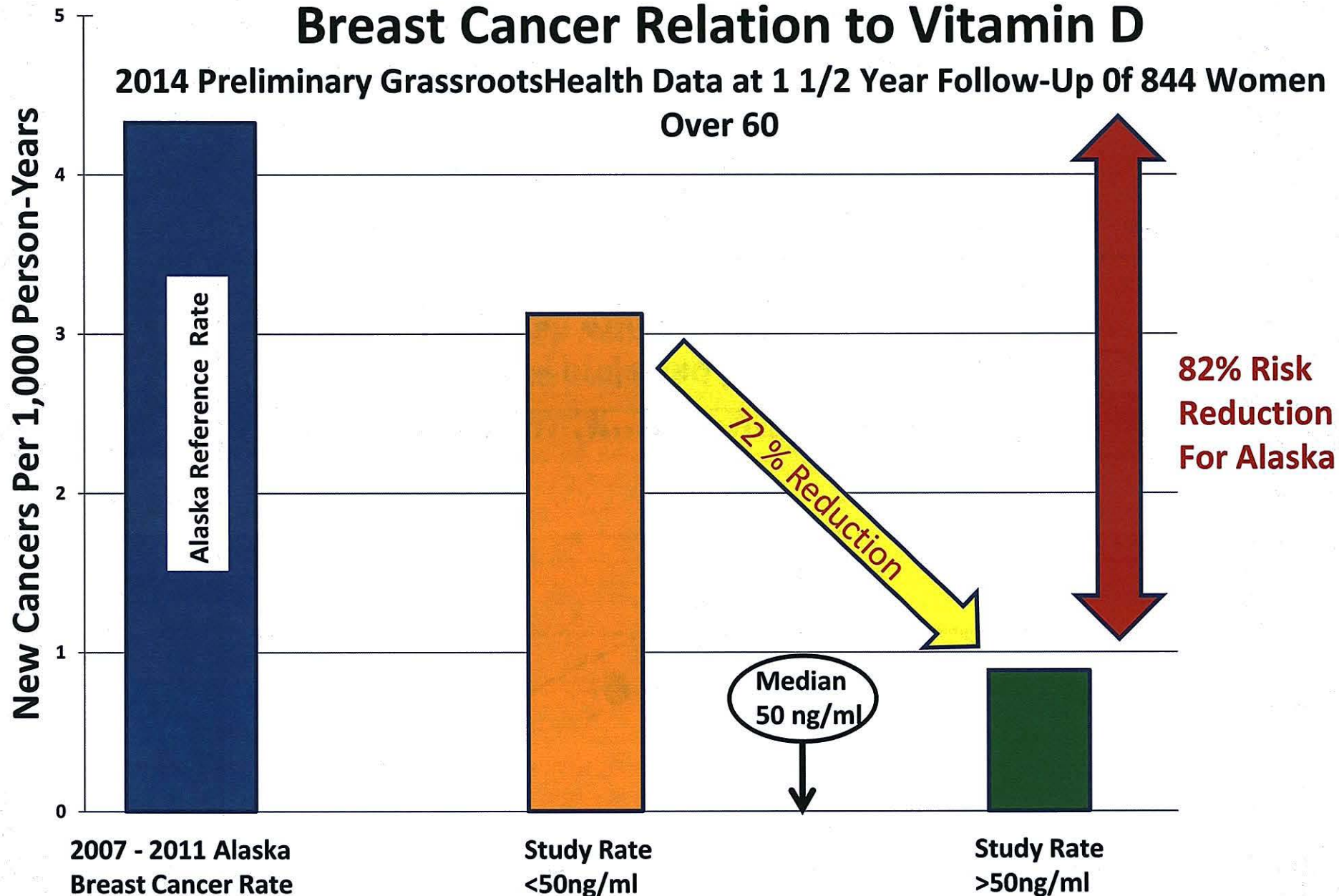
[Slide by Cedric F. Garland, et al. University of California San Diego]



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

# Breast Cancer Relation to Vitamin D

2014 Preliminary GrassrootsHealth Data at 1 1/2 Year Follow-Up Of 844 Women Over 60



Hazard ratio of breast cancer for those with serum 25(OH)D <50ng/ml was 5.1 times more compared to those with  $\geq$  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**

# PRETERM BIRTHS



### March of Dimes 2020 Goal

- Reduce preterm births to no more than 9.6% of live births.
- For more information, see [here](#).

7% has already been achieved

## Alaska

Find maternal and infant health data on a state level, or by county or city. Narrow your results or compare with another region.

**Location:** Alaska edit

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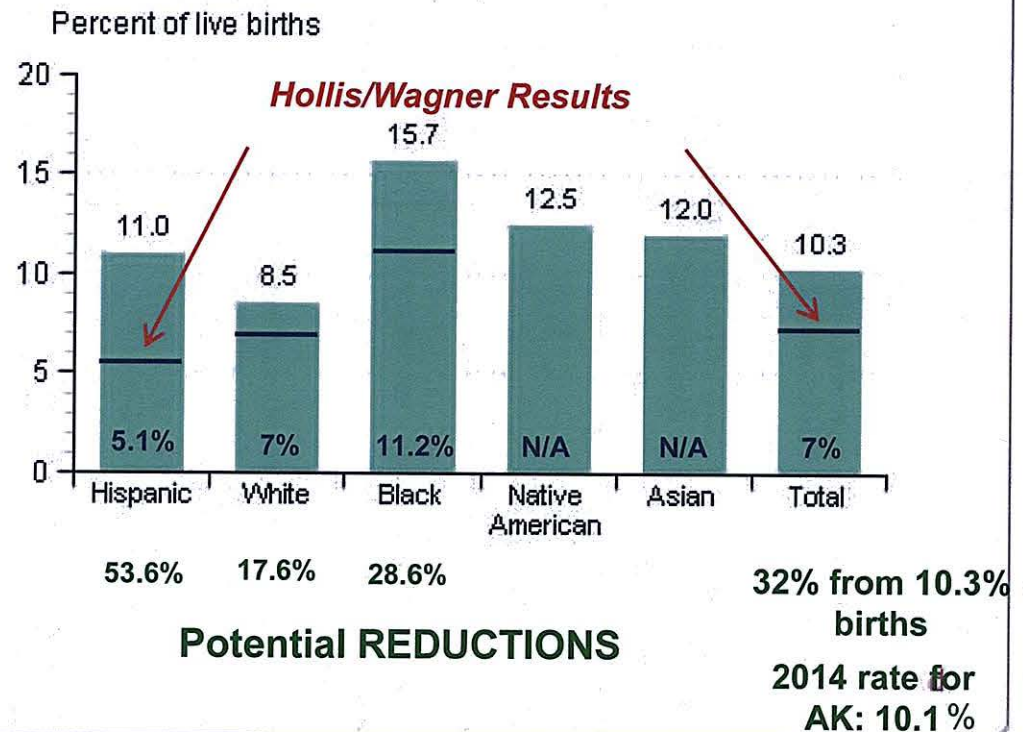
**Topic:** Preterm by race/ethnicity edit

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**Format:** Bar Graph edit

[view tray](#) slides (0)

**Preterm by race/ethnicity: Alaska, 2009-2011 Average**





## GRASSROOTSHEALTH

A Public Health Promotion Organization

### Protect Our Children *NOW!*

*A community outreach program to reduce the incidence of preterm births quickly, easily, and safely by attending to solving the vitamin D deficiency epidemic through the engagement of pregnant women in a value changing program of Good Health vs 'Treating Illness'*

Approximately 1300 infants will be born prematurely in Alaska in 2014 per the March of Dimes. Fully 25-50% of these in the state, 325-650 babies and their families, could possibly have this trauma prevented with vitamin D supplementation to the pregnant mother. Premature births are closely associated with cerebral palsy, mental impairment and permanent hearing loss among other deficiencies.

The March of Dimes estimates that the cost of each premature infant is \$55,000, adding up to a total annual cost of \$72MM of which \$18-36MM could likely be saved (on an annual basis). Data from randomized trials and others works from Dr. Wagner et al. showed a potential reduction of 50% in preterm births and significant reductions in preeclampsia and gestational diabetes as well as other complications of pregnancy. The problem now is getting the results into practice quickly vs waiting the standard 15-25 years.

Solving this problem requires nothing less than *Changing Cultural Values*, from 'Early Detection' to 'Primary Prevention'; from 'Affordable Care' to 'Good Health'; from individuals 'Taking Advice' of physicians to 'Consultation' with them. In order to accomplish this, the timing is perfect to link a new, highly accepted technology (internet application) to the new value of HEALTH through the environment of 'MyOWNHealth™' which captures all the essential ingredients of change: the science, the proven recommendations for pregnancy, clear methods for setting priorities for the individual, personal feedback and rewards for performance, a process for total engagement from learning through personal reward systems. This is a personal portal for the patient.

Behind the scenes, information is tracked by the system to provide information to the providers, the insurers, the scientists about what's working, what needs changing, i.e., a complete feedback loop to perfect the process. This will improve processes as well as strengthen public health.

A full demonstration of this process, to serve as a 'seed' for an entire community, has been developed by an international non-profit public health promotion organization, GrassrootsHealth, in conjunction with the leading researcher, Dr. Carol L. Wagner of the Medical University of South Carolina as the Principal Designer/Leader. They have in place not only a vitamin D testing program for the mothers and infants, but all the pieces of the MyOWNHealth™ system: simple, interactive educational programs for participants and physicians, engaging games and reward systems, programs to track the progress of healthy behavioral changes, management feedback to provide ongoing enhancements to the process.

This community project will involve the active participation of about 500 pregnant women. With the 500 women participating, there could be 25 children saved this problem with a potential cost savings of \$1,375,000 for this group alone in the first implementation.

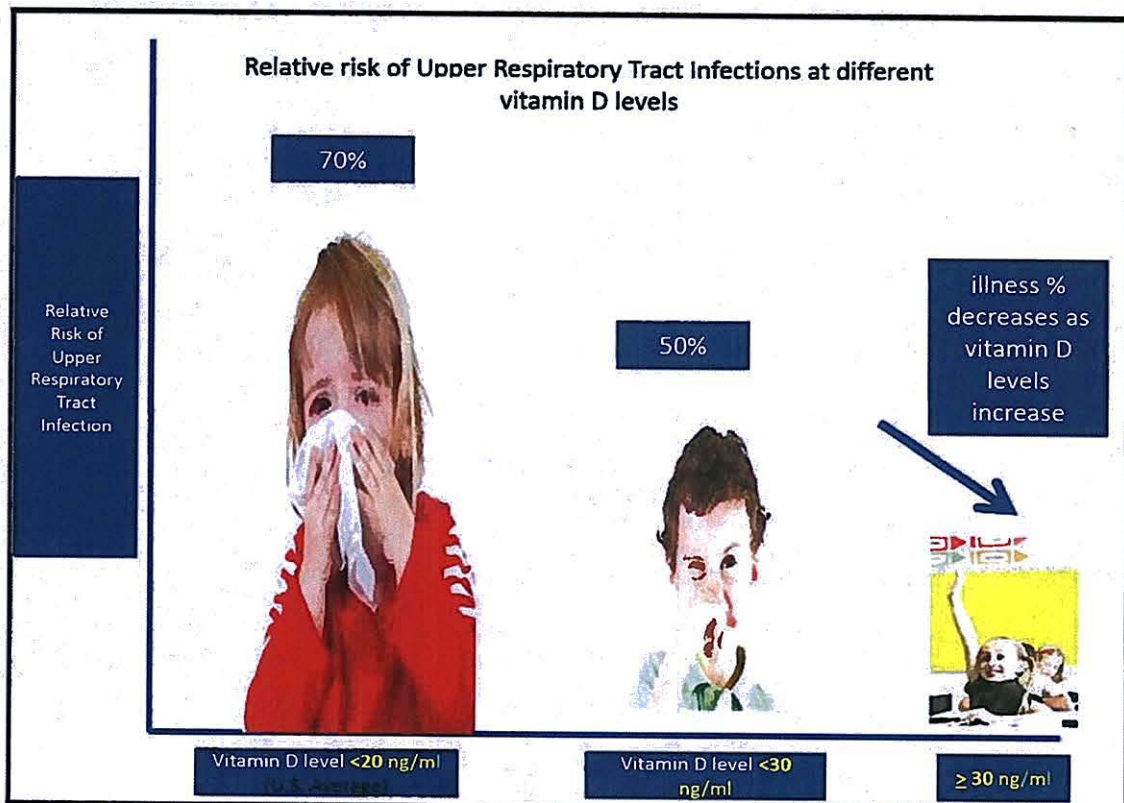
Next steps to explore this program would include a meeting with Carole Baggerly, director of GrassrootsHealth and Dr. Wagner to highlight the details of a project plan for the community site.

- Approximate number of births per year in Alaska = 11,000
- Assumption: 500 births per year to State of Alaska Employees, Retirees and Dependents
- For each 500 pregnancies in the Alaska insured and dependent category with vitamin D sufficiency 25 preterm births avoided
- Savings to the state by avoiding 25 preterm births = **\$1,375,000**

# 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

# Vitamin D<sub>3</sub> supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study

Peter Bergman,<sup>1,2,3</sup> Anna-Carin Norlin,<sup>2,4</sup> Susanne Hansen,<sup>2</sup> Rokeya Sultana Rekha,<sup>5</sup> Birgitta Agerberth,<sup>5</sup> Linda Björkhem-Bergman,<sup>6</sup> Lena Ekström,<sup>6</sup> Jonatan D Lindh,<sup>6</sup> Jan Andersson<sup>3</sup>

**To cite:** Bergman P, Norlin A-C, Hansen S, *et al*. Vitamin D<sub>3</sub> supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study. *BMJ Open* 2012;2:e001663. doi:10.1136/bmjopen-2012-001663

► Prepublication history and additional material for this paper are available online. To view these files please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2012-001663>).

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Accepted 15 November 2012

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PB and AGN contributed equally to this study.

For numbered affiliations see end of article.

Correspondence to Dr Peter Bergman; [peter.bergman@ki.se](mailto:peter.bergman@ki.se)

## ABSTRACT

**Background:** Low serum levels of 25-hydroxyvitamin D<sub>3</sub> are associated with an increased risk of respiratory tract infections (RTIs). Clinical trials with vitamin D<sub>3</sub> 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<sub>3</sub> on infections.

**Objective:** To investigate if supplementation with vitamin D<sub>3</sub> 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<sub>3</sub> (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<sub>3</sub>, 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<sub>3</sub> may reduce disease burden in patients with frequent RTIs.

## ARTICLE SUMMARY

### Article focus

- Recent evidence suggests that vitamin D<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> 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<sub>3</sub> was given to patients with an increased susceptibility to infections for 1 year.
- The main conclusion is that vitamin D<sub>3</sub> supplementation reduces symptoms and antibiotic consumption among patients with an increased frequency of respiratory tract infections. Thus, vitamin D<sub>3</sub> supplementation may be an alternative strategy to reduce antibiotic use among patients with recurrent respiratory tract infections.

### Strengths and limitations of this study

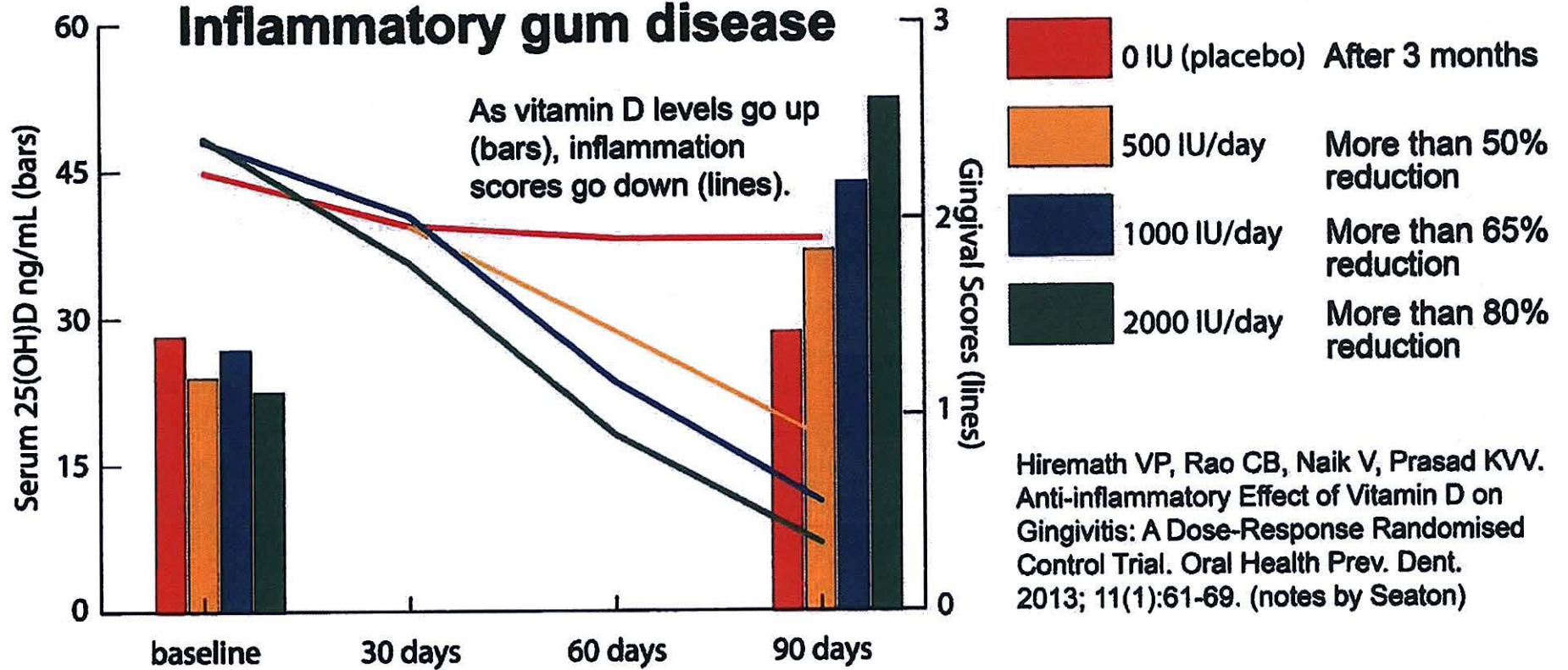
- A high daily dose of vitamin D<sub>3</sub> was used, the study time was a full year covering all seasons and patients with an increased frequency of respiratory tract infections were studied.
- A single study centre, small sample size (n=140) and a selected group of patients.

## INTRODUCTION

Vitamin D was discovered when it was noted that rachitic children were improved by exposure to sunlight.<sup>1</sup> It was later shown by Holick *et al*<sup>2</sup> that vitamin D<sub>3</sub> is synthesised in the skin under the influence of ultraviolet light. Vitamin D<sub>3</sub> is further hydroxylated in the liver

# INFLAMMATION

# Inflammatory gum disease



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](http://www.open.hqsc.govt.nz).

## **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**

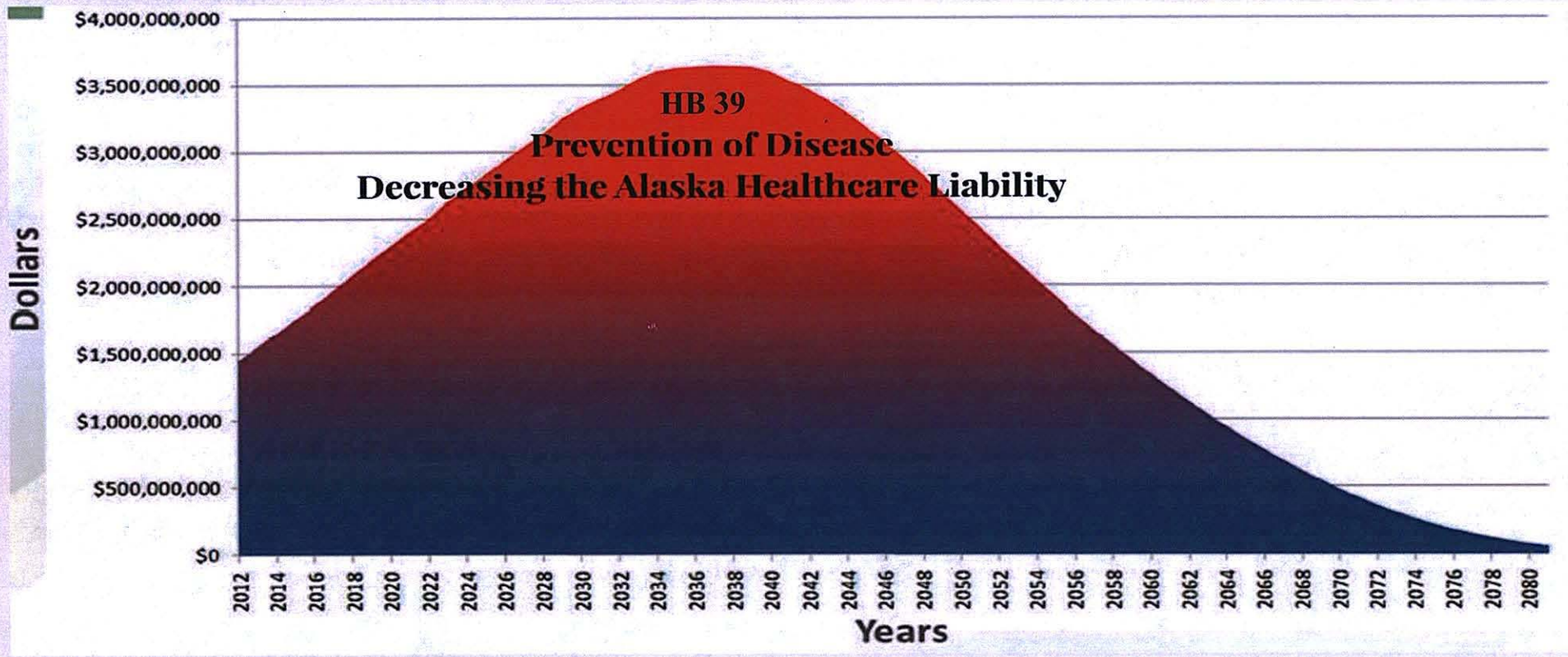
This section requires the Department of Administration, to the extent legal and reasonably practicable, to implement the recommendations of the Advisory Committee on Wellness and reduce the escalation of health care costs. This section of statute applies to state life and health insurance plans.

#### **Section 3**

This section requires the Department of Administration, to the extent legal 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.






## \$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%.





# Why are we here?

*The State of Alaska is a significant health care consumer.*

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

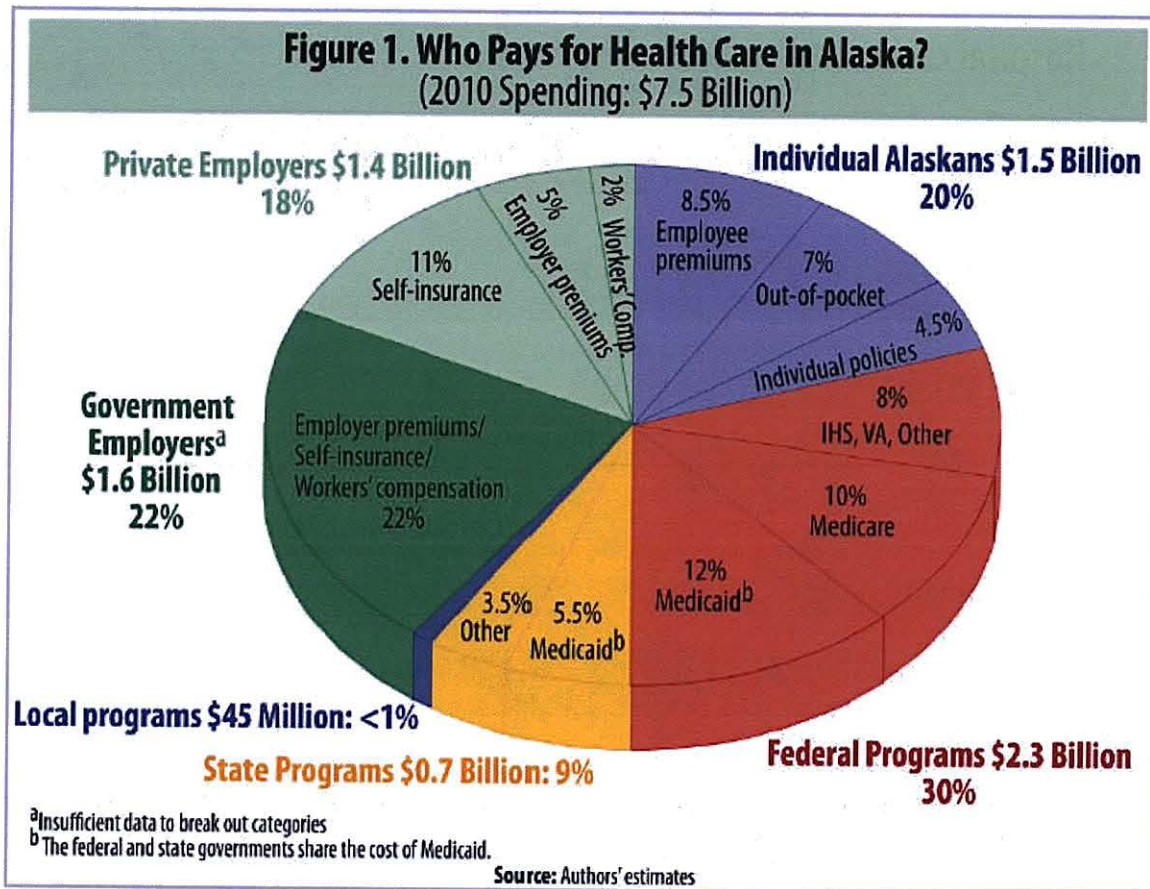
The state also spends money on health care for inmates, state employees who are members of union health trusts and for state workers' compensation claims.

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

By Mark A. Foster and Scott Goldsmith

UA Research Summary No. 18 • August 2011

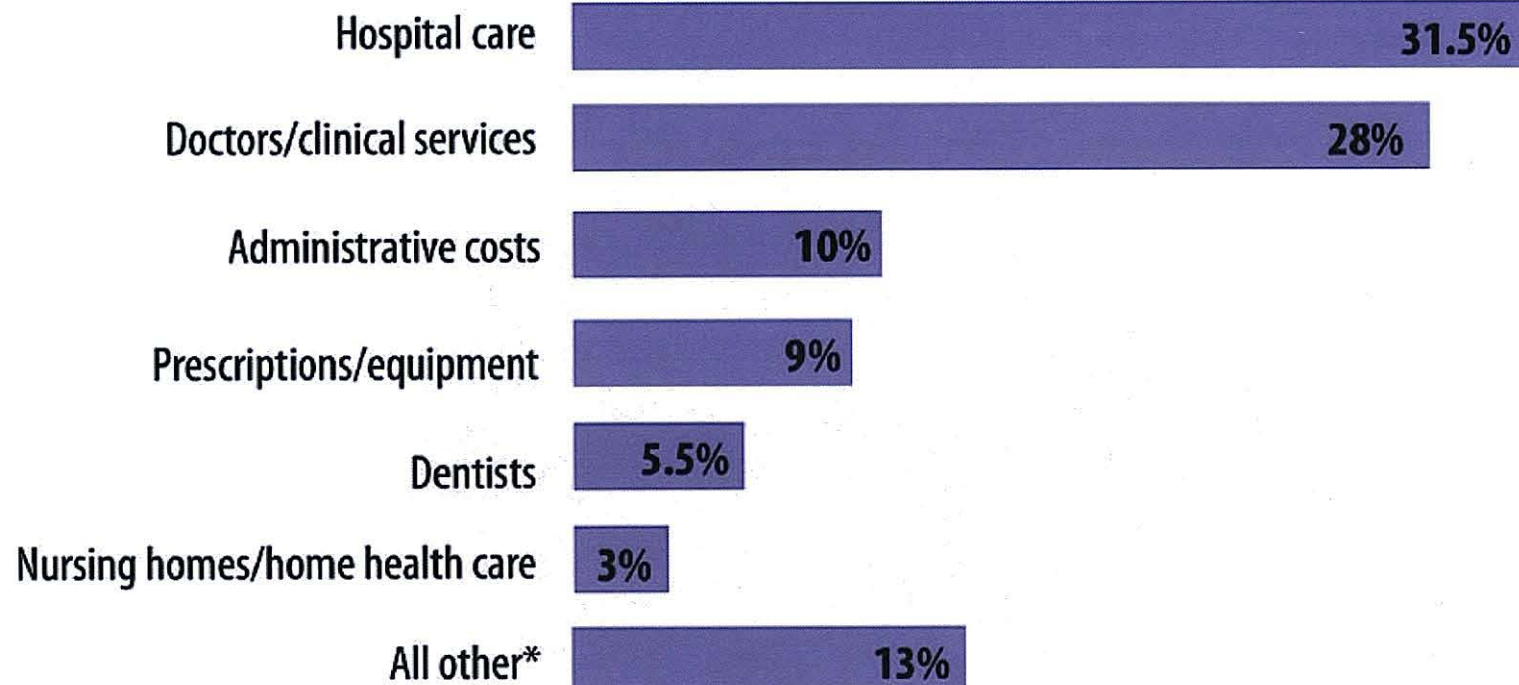
Institute of Social and Economic Research • University of Alaska Anchorage



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.

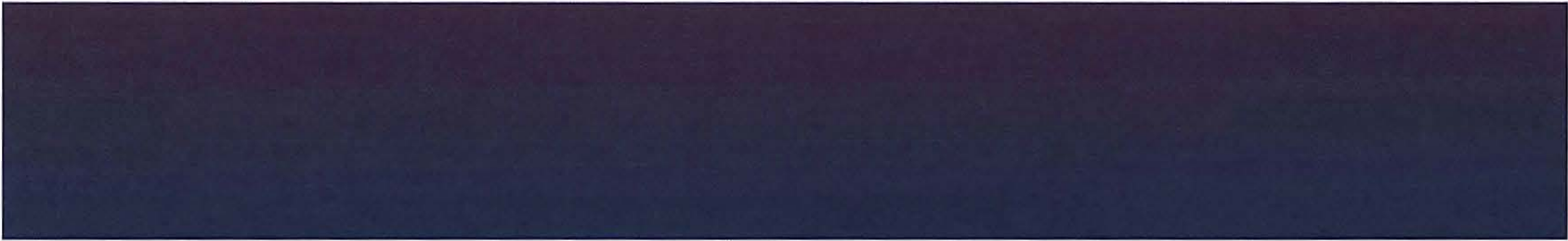
Source: Mark A. Foster and Associates estimates, based on Centers for Medicare and Medicaid Services, National Health Expenditure accounts



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.



4th Quarter Report 2013

**ACTIVE PLAN**

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

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

## RETIREE PLAN



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%

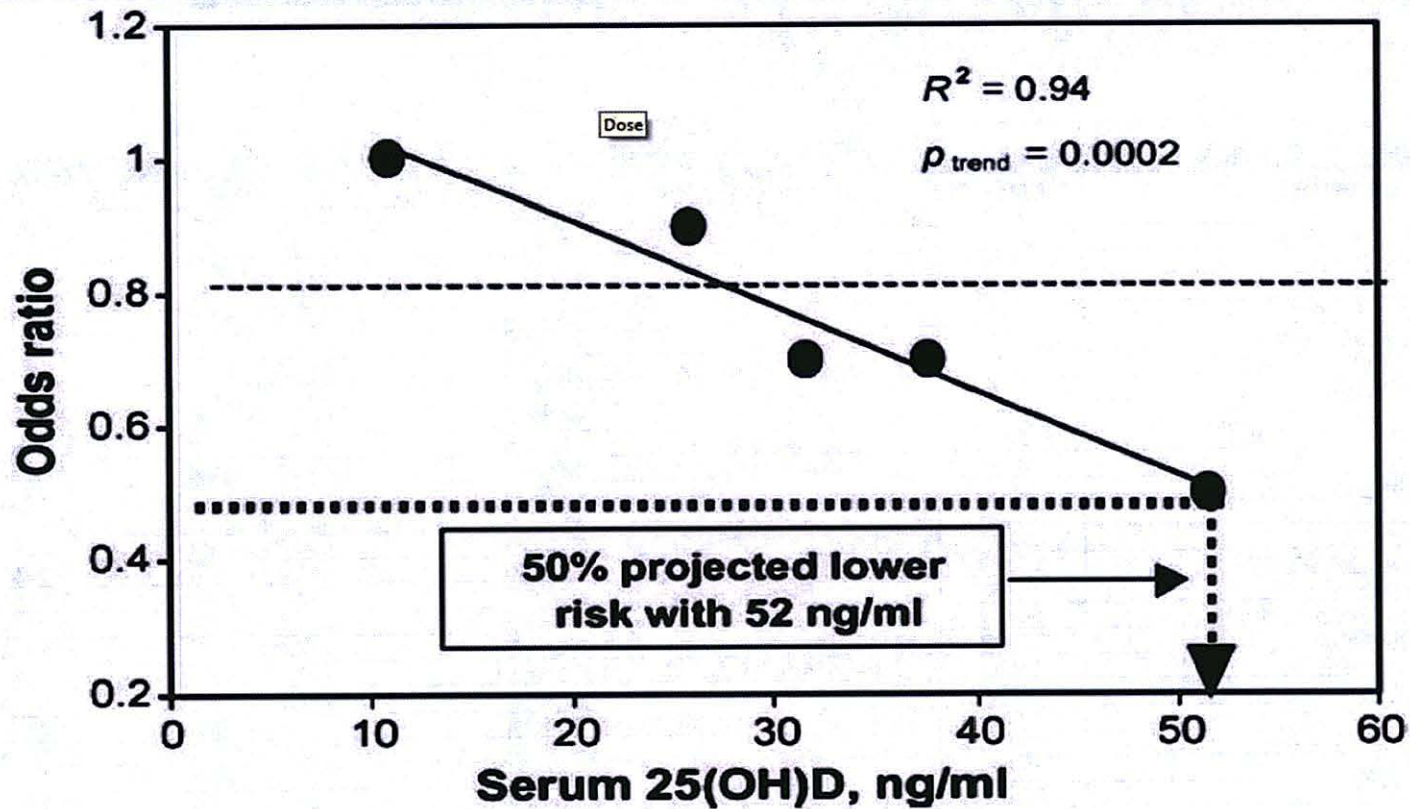
Aggregate Risk Summary				
Risk Drivers	# Members	Avg Risk Contribution	Contribution to Forecast	Risk Contribution
Demographics	65376	SENIORS SKIN, FRACTURES, FALLS \$454	\$29,702,943	2.90% X
Acute Respiratory Disorders	9520	TUBERCULOSIS \$1,669	\$15,893,121	1.55% X
Arrhythmia Disorders	5170	\$2,860	\$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%**

AlaskaCare Retiree Plan - 4th Quarter Report 2013

Notes in red by office of Rep. Seaton

# Meta-analysis of breast cancer risk



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:**

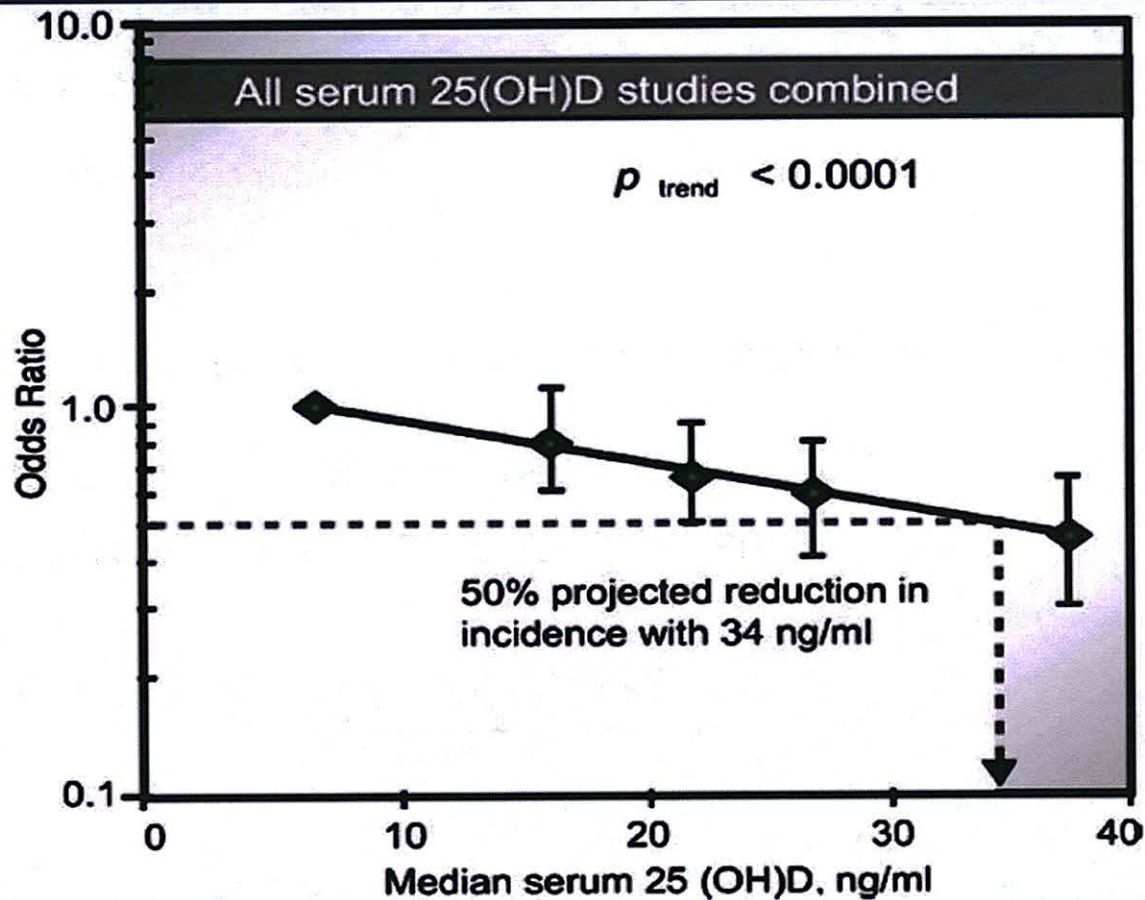
**\$3,024,312**

**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.<sup>1,4-7</sup> 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**

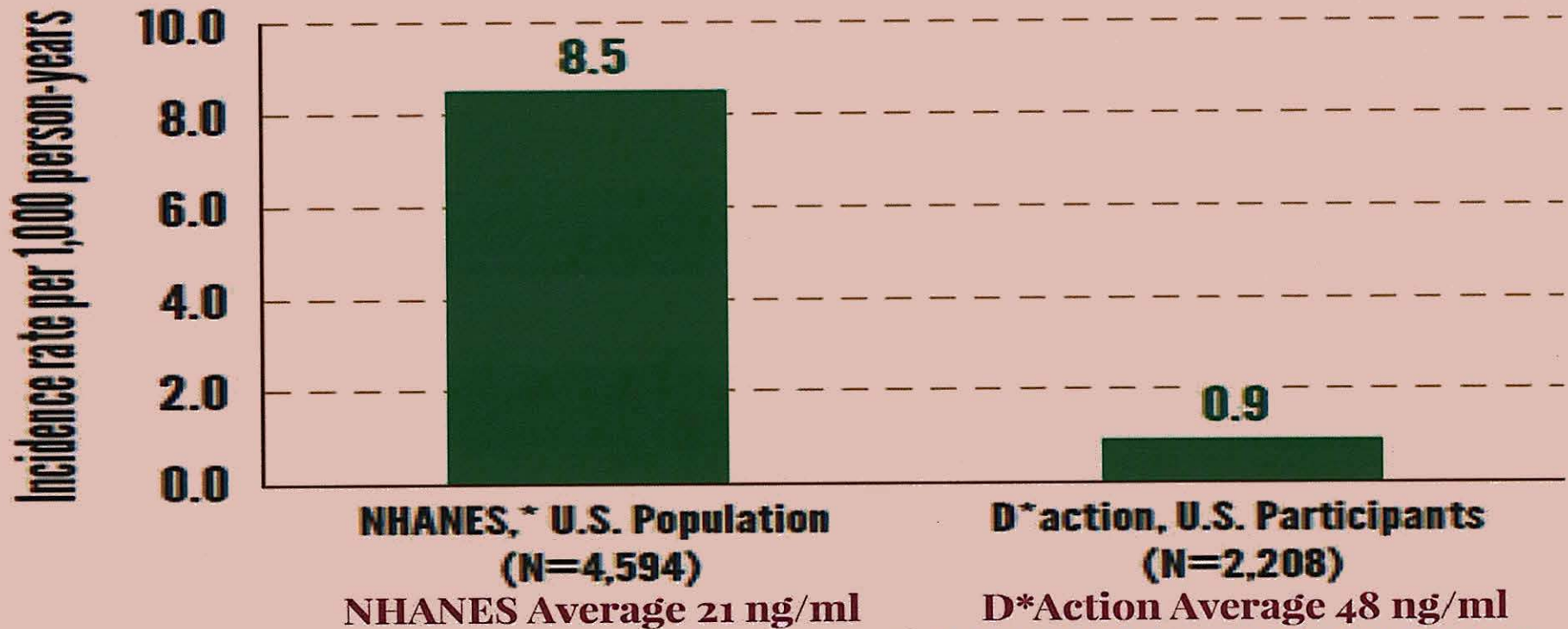
**\$1,962,950**

**(meta-analysis Gorham et. al.)**

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# TYPE 2 DIABETES

## Diabetes Incidence: Comparing NHANES\* and D\*action (18+ years)



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

\*\*RATE RATIO = 9.7 (P=0.0002)

Chart Date 8/6/13

© 2013 GrassrootsHealth

Preliminary data, not yet published.

Vitamin **D\*action**



**GrassrootsHealth**  
A Public Health Promotion Organization

[www.grassrootshealth.net](http://www.grassrootshealth.net)

**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.)**



### March of Dimes 2020 Goal

- Reduce preterm births to no more than 9.6% of live births.
- For more information, see [here](#).

7% has already been achieved

## Alaska

Find maternal and infant health data on a state level, or by county or city. Narrow your results or compare with another region.

Location: Alaska edit

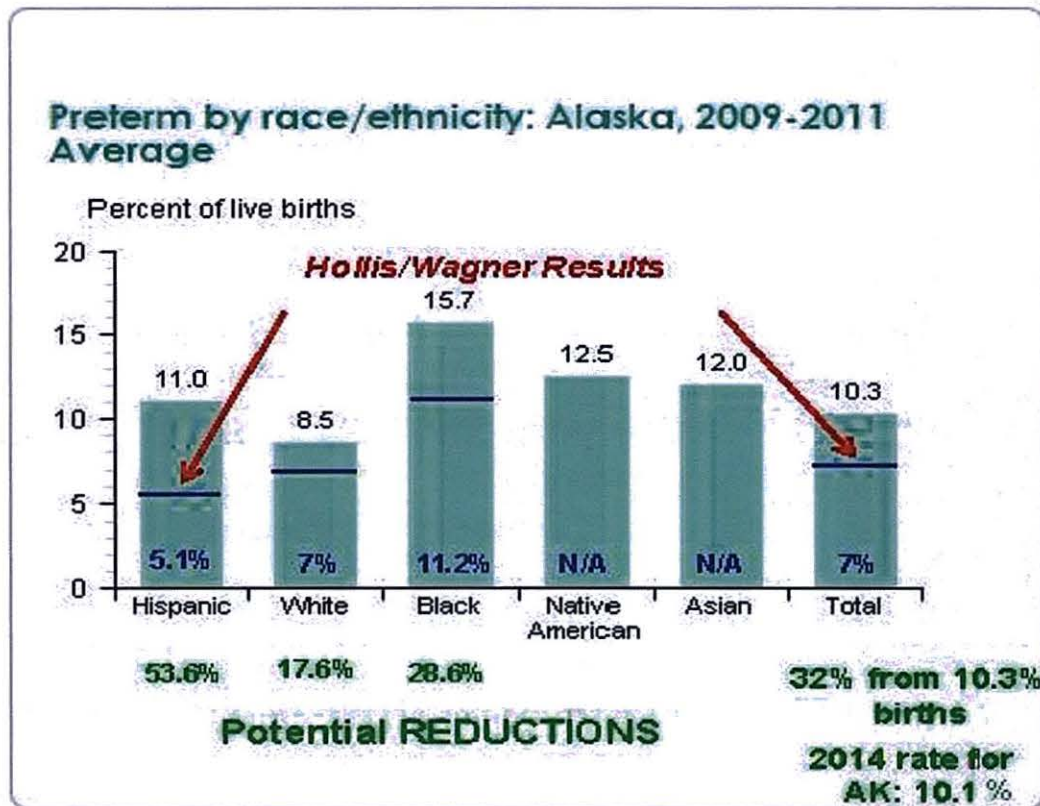
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Topic: Preterm by race/ethnicity edit

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Format: Bar Graph edit


slides (0)



[Slide produced by GrassRoots Health, Protect our Children Now!]

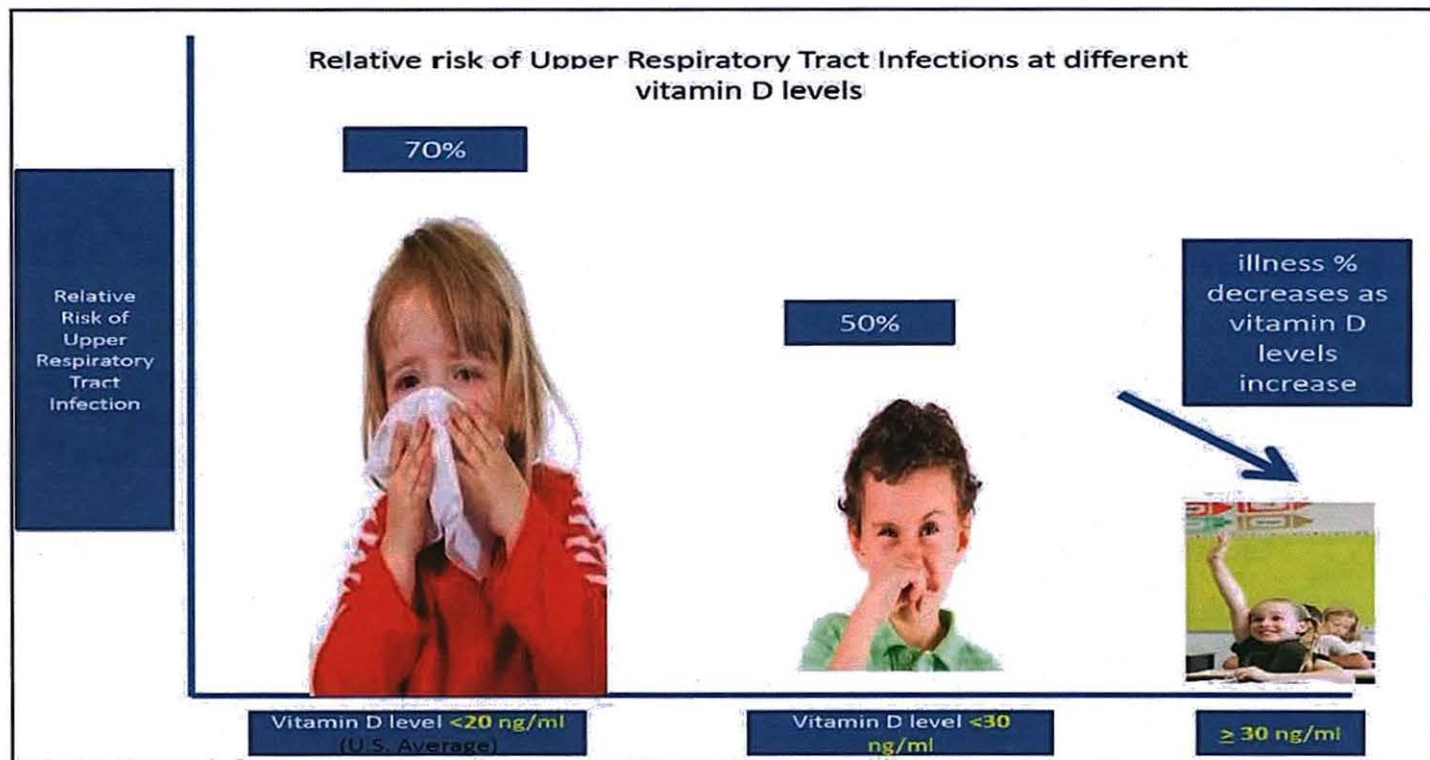


share | email | print | add to tray |

- 
- Approximate number of births per year in Alaska = 11,000
  - Assumption: 500 births per year to State of Alaska Employees, Retirees and Dependents
  - For each 500 pregnancies in the Alaska insured and dependent category with vitamin D sufficiency 25 preterm births avoided
  - Savings to the state by avoiding 25 preterm births = \$1,375,000
- 

## Upper Respiratory Tract Infections

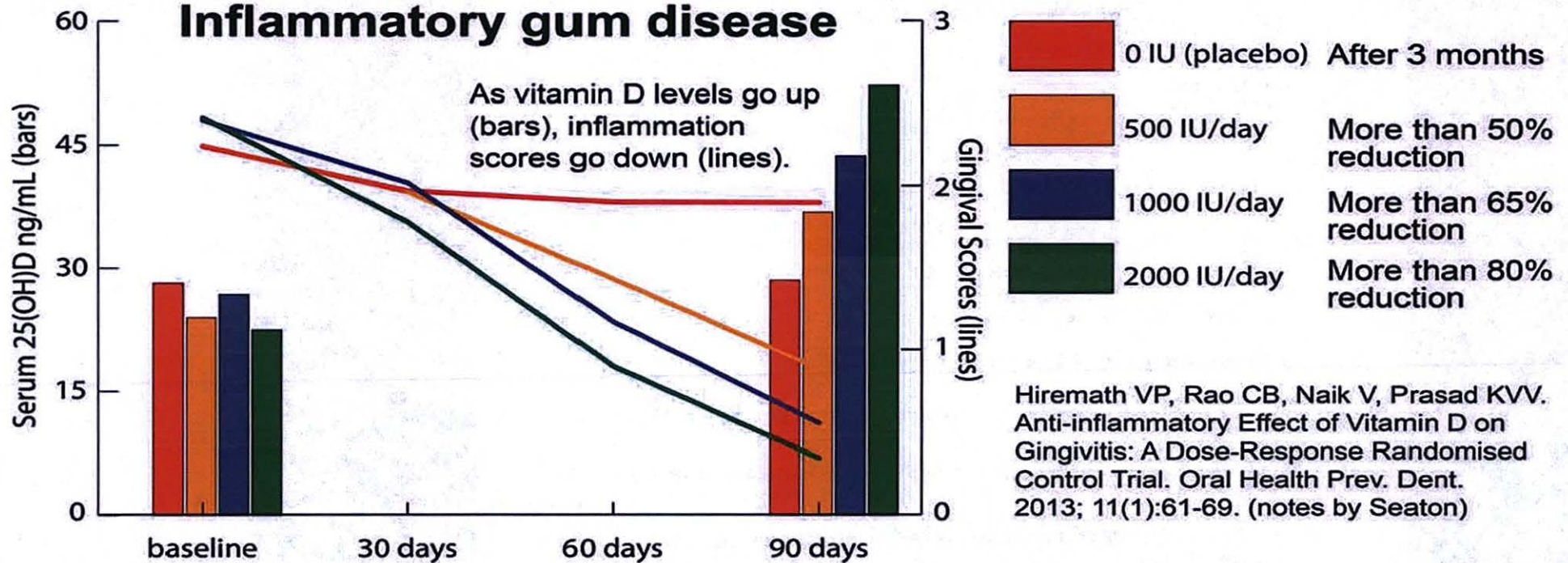
Recently, a study was conducted with seven hundred forty-three children ages 3-15 in a Canadian Hutterite Community. **The findings of the study show that children with higher vitamin D blood levels had a 50% lower relative risk of contracting an Upper Respiratory Tract infection.** Those children at 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



**HOUSE BILL NO. 39**

IN THE LEGISLATURE OF THE STATE OF ALASKA

TWENTY-NINTH LEGISLATURE - FIRST SESSION

BY REPRESENTATIVE SEATON

Introduced: 1/9/15

Referred: Prefiled

**A BILL**

**FOR AN ACT ENTITLED**

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

3 **BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF ALASKA:**

4 \* **Section 1.** The uncodified law of the State of Alaska is amended by adding a new section  
5 to read:

6 **LEGISLATIVE FINDINGS AND INTENT.** (a) The legislature finds that

7 (1) individual Alaskans and the state share the burden of increasing health care  
8 and insurance costs resulting from avoidable disease in humans;

9 (2) state policy should focus more on avoiding disease and maintaining good  
10 health in the state's population;

11 (3) the state relies partly on federal one-size-fits-all human health policy  
12 recommendations, creating federal overreach into the state's administration of health policy;

13 (4) the state's human health policies should incorporate peer-reviewed  
14 scientific studies that illustrate health-related differences between the population of the state

11 providing health care benefits to persons who are covered by a policy of group health  
12 insurance obtained under AS 39.30.090(a) or 39.30.091(a) to a rate that does not exceed two  
13 percent annually.

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

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

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

23 (b) To the greatest extent legally and reasonably practicable, the Department  
24 of Administration shall work to hold the escalation of health care costs to less than two  
25 percent annually by administering policies of group health insurance obtained under



## KENAI PENINSULA BOROUGH SCHOOL DISTRICT

### Office of Superintendent

Dr. Steve Atwater, Superintendent of Schools  
148 North Binkley Street Soldotna, Alaska 99669-7553  
Phone (907) 714-8888 Fax (907) 262-9132

March 6, 2014

Representative Paul Seaton  
State Capitol, Room 102  
Juneau, AK 99801-1182

Dear Representative Seaton,

I am writing on behalf of the Kenai Peninsula Borough School District to support House Bill 356. If passed, the bill will create an Advisory Committee on Wellness which will make recommendations to the Commissioner of Administration on ways to decrease the incidence of disease in Alaska. The intent of the bill is to implement policies to keep Alaska state employees healthy by preventing disease, rather than waiting to react once people are sick. KPBSD welcomes this proactive approach and recognizes that it is a necessary step in ensuring a healthy workforce as well as reducing the amount of funds dedicated to health care.

The cost of health care for my district's employees is increasing. In FY09 the total spent on employee health care was \$15,376,426 while last year it was \$21,541,380. This 40% increase in four years is alarming and unsustainable. KPBSD is thus pleased to support this bill which can help stem increases in district funds to health care.

Please contact me if you require further information for why KPBSD supports passage of HB 356.

Sincerely,

Steve Atwater, Ph.D.  
Superintendent of Schools

# 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.

© 2013 Mayo Foundation for Medical Education and Research ■ 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.<sup>1,2</sup> 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.<sup>1-4</sup> 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.<sup>5</sup>

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.<sup>2,6,7</sup> In addition, critical windows of exposure to adequate vitamin D levels during fetal maturation remain to be defined<sup>5,6</sup> owing, in part, to the lack of well-designed controlled clinical trials with long-term follow-up.<sup>5-7</sup>

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<sub>2</sub>, D<sub>3</sub>, 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.<sup>2,7</sup>

During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D<sub>3</sub>. The 7-DHC is present in all the layers of human skin.<sup>7-9</sup> Approximately 65% of 7-DHC is found in the epidermis, and greater than 95% of the previtamin D<sub>3</sub> that is produced is in the viable epidermis and, therefore, cannot be removed from the skin when it is washed.<sup>9</sup> Once previtamin D<sub>3</sub> 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<sub>3</sub> (Figure 1).<sup>7,8</sup> The cutaneous production of previtamin D<sub>3</sub> is regulated. Solar photoproducts (tachysterol and

lumisterol) inactive on calcium metabolism are produced at times of prolonged exposure to solar UV-B radiation, thus preventing sun-induced vitamin D intoxication.<sup>7,8</sup> Vitamin D<sub>3</sub> is also sensitive to solar irradiation and is, thereby, inactivated to suprasterol 1 and 2 and to 5,6-trans-vitamin D<sub>3</sub>.<sup>7</sup> Cutaneous vitamin D<sub>3</sub> production is influenced by skin pigmentation, sunscreen use, time of day, season, latitude, altitude, and air pollution.<sup>1,2,7,8</sup> 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<sub>3</sub> is made in the skin during winter.<sup>10,11</sup> 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<sub>3</sub> synthesis occurs only between approximately 10 AM and 3 PM.<sup>1,11</sup> Similarly, in urban areas, such as Los Angeles, California, and Mexico City, Mexico, where nitrogen dioxide and ozone levels are high, few vitamin D<sub>3</sub>-producing UV-B photons reach the people living in these cities.<sup>7,11</sup> Similarly, because glass absorbs all UV-B radiation, no vitamin D<sub>3</sub> is produced in the skin when the skin is exposed to sunlight that passes through glass.

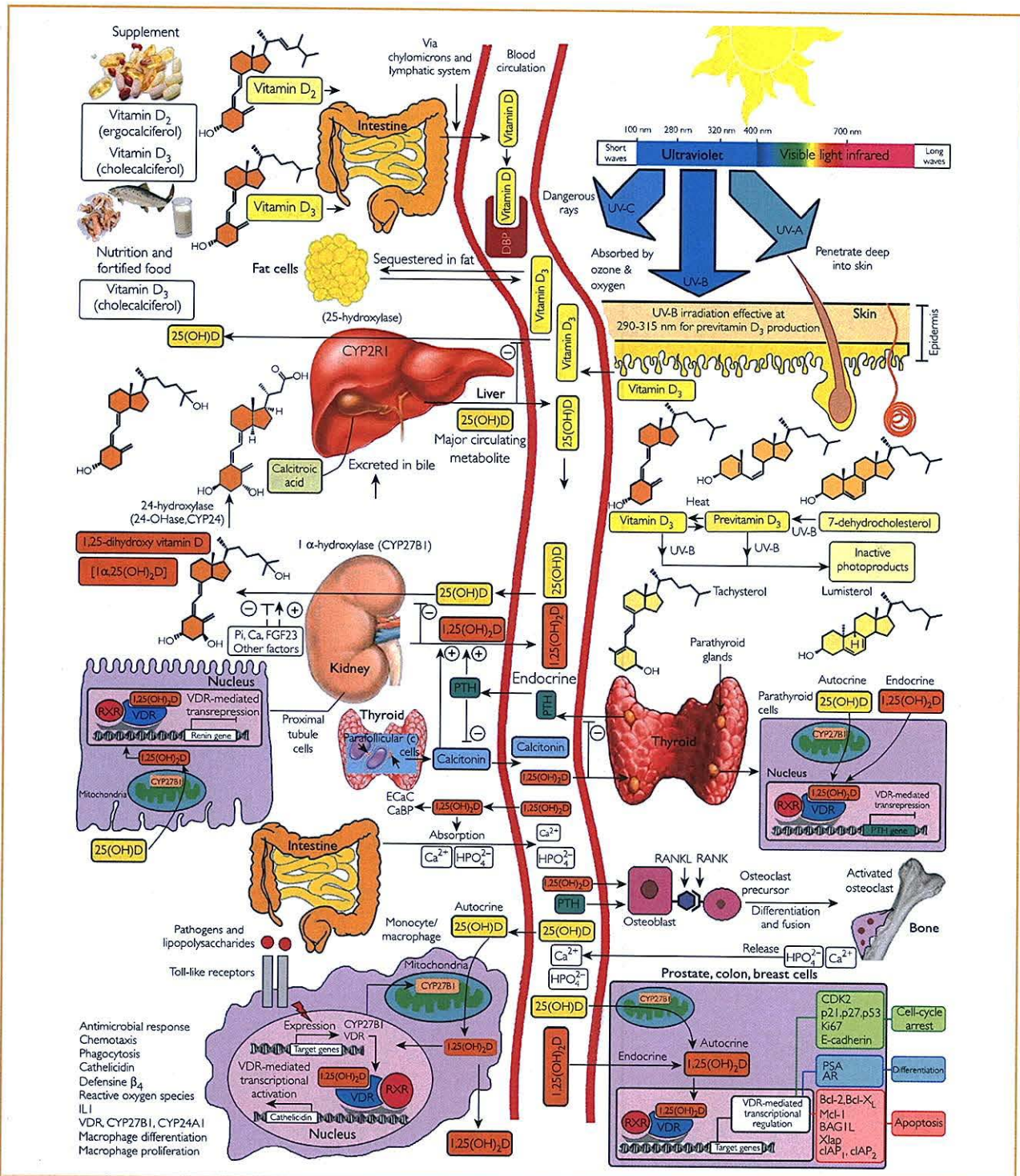
Once formed, vitamin D<sub>3</sub> is ejected out of the keratinocyte plasma membrane and is drawn into the dermal capillary bed by the vitamin D binding protein (DBP).<sup>7,8</sup> Vitamin D that is ingested is incorporated into chylomicrons, which are released into the lymphatic system, and enters the venous blood,<sup>2,7</sup> where it binds to DBP and lipoproteins transported to the liver.<sup>1,2,7</sup> Vitamin D<sub>2</sub> and vitamin D<sub>3</sub> 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.<sup>1,2,7</sup> This metabolite undergoes further hydroxylation by the 25(OH)D-1 $\alpha$ -hydroxylase (CYP27B1) in the kidneys to form the secosteroid hormone 1 $\alpha$ ,25-dihydroxyvitamin D [1,25(OH)<sub>2</sub>D] (Figure 1).<sup>2,7,12</sup> The 25(OH)D bound to DBP is filtered in the kidneys and is reabsorbed in the proximal renal tubules by megalin cubilin receptors.<sup>6,12</sup> The renal

#### 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.

1 $\alpha$ -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)<sub>2</sub>D itself.<sup>7,13,14</sup>

The 1,25(OH)<sub>2</sub>D performs many of its biologic functions by regulating gene transcription through a nuclear high-affinity vitamin D receptor (VDR).<sup>15,16</sup> 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.<sup>2,7,17</sup> 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.<sup>2,16</sup> A recent microarray study on the influence of vitamin D status and vitamin D<sub>3</sub> supplementation on genome-wide expression in white blood cells before and after vitamin D<sub>3</sub> 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.<sup>17</sup> 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



**FIGURE 1.** Schematic representation of the synthesis and metabolism of vitamin D for skeletal and nonskeletal function. 1-OHase = 25-hydroxyvitamin D-1 $\alpha$ -hydroxylase; 24-OHase = 25-hydroxyvitamin D-24-hydroxylase; 25(OH)D = 25-hydroxyvitamin D; 1,25(OH)<sub>2</sub>D = 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- $\kappa$ B; RANKL = receptor activator of the NF- $\kappa$ B ligand; RXR = retinoic acid receptor; TLR2/1 = Toll-like receptor 2/1; VDR = vitamin D receptor; vitamin D = vitamin D<sub>2</sub> or vitamin D<sub>3</sub>. Copyright Holick 2013, reproduced with permission.

more than 80 pathways linked to cancer, autoimmune disorders, and cardiovascular disease, which have been associated with vitamin D deficiency.<sup>17</sup>

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).<sup>2,7</sup> The  $1,25(\text{OH})_2\text{D}$  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%.<sup>7</sup> It also interacts with VDR in osteoblasts to stimulate a receptor activator of nuclear factor  $\kappa\text{B}$  ligand, which, in turn, interacts with receptor activator of nuclear factor  $\kappa\text{B}$  on immature preosteoclasts, stimulating them to become mature bone-resorbing osteoclasts (Figure 1).<sup>7,18</sup> The mature osteoclast removes calcium and phosphorus from the bone to maintain blood calcium and phosphorus levels. In the kidneys,  $1,25(\text{OH})_2\text{D}$  stimulates calcium reabsorption from the glomerular filtrate.<sup>2,7</sup>

The VDR is present in most tissues and cells in the body.<sup>1,2,7,19-25</sup> 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  $1,25(\text{OH})_2\text{D}$ .<sup>1,2,7,19-25</sup> This production probably depends on the availability of circulating  $25(\text{OH})\text{D}$ , indicating the biological importance of sufficient blood levels of this vitamin D metabolite.<sup>2,15,26</sup>

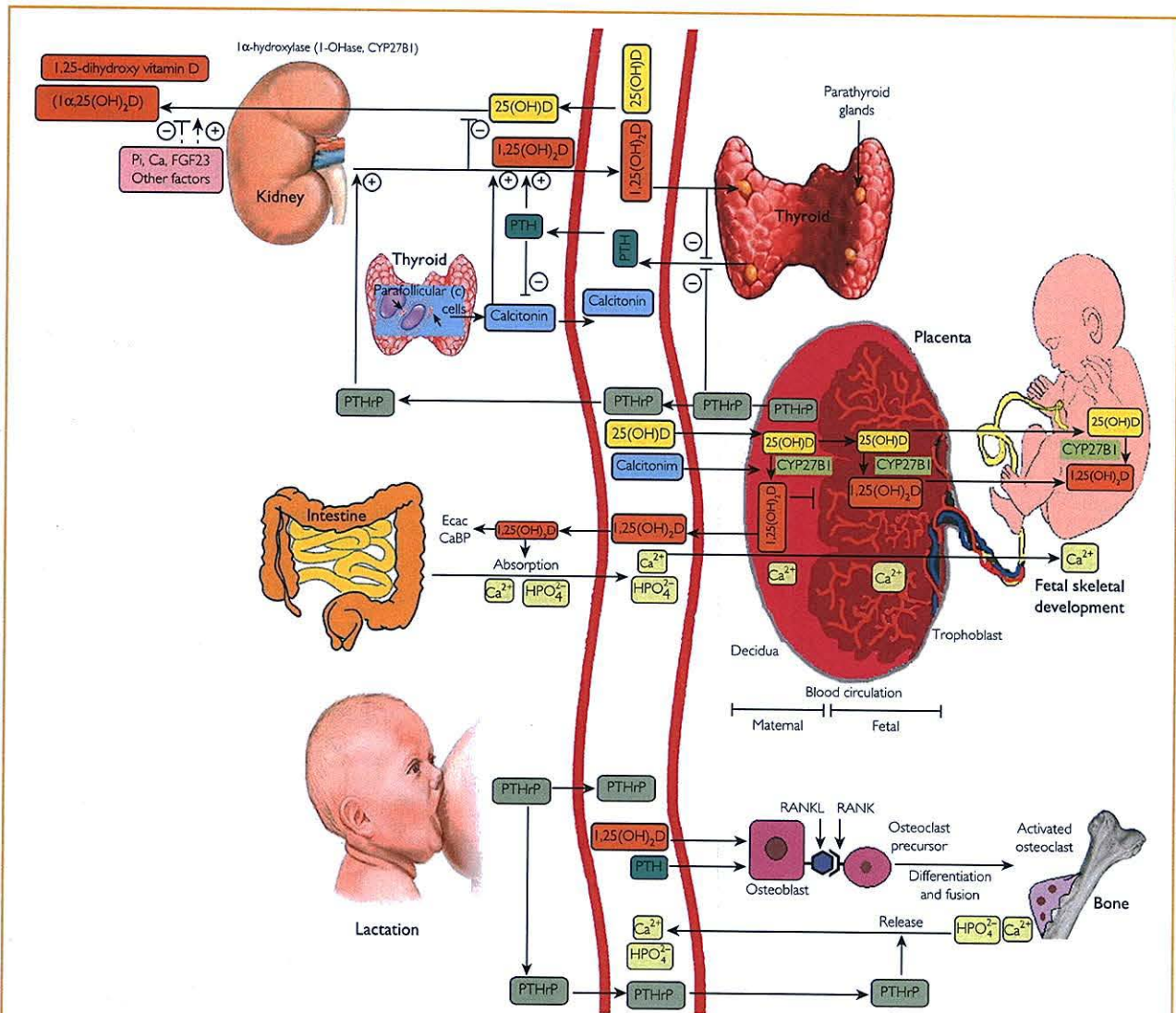
The estimated 2000 genes that are directly or indirectly regulated by  $1,25(\text{OH})_2\text{D}$ <sup>2,7,17-24,26</sup> have a wide range of proven biological actions, including inhibiting cellular proliferation and inducing terminal differentiation, inhibiting angiogenesis, stimulating insulin production, inducing apoptosis, inhibiting renin production, and stimulating macrophage cathelicidin production.<sup>1,2,7,16,17,26</sup> In addition,  $1,25(\text{OH})_2\text{D}$  stimulates its own destruction in the kidneys and in cells that have a VDR and responds to  $1,25(\text{OH})_2\text{D}$  by enhancing expression of the  $25(\text{OH})\text{D}$ -24-hydroxylase (CYP24A1) to metabolize  $25(\text{OH})\text{D}$  and  $1,25(\text{OH})_2\text{D}$  into water-soluble inactive forms that are excreted in the bile (Figure 1).<sup>1,7,19,27</sup>

## VITAMIN D METABOLISM DURING PREGNANCY

Vitamin D metabolism is enhanced during pregnancy and lactation. The placenta is formed at 4 weeks of gestation.<sup>2,25</sup> From this time to term,  $25(\text{OH})\text{D}$  is transferred across the placenta, and the fetal cord blood concentration of  $25(\text{OH})\text{D}$  is correlated with the mother's concentration.<sup>27</sup> However, the active metabolite  $1,25(\text{OH})_2\text{D}$  does not readily cross the placenta.<sup>25,27</sup> The fetal kidneys and the placenta provide the fetal circulation with  $1,25(\text{OH})_2\text{D}$  by expressing CYP27B1 (Figure 2).<sup>28</sup>

The maternal (decidual) and fetal placental (trophoblastic) components of the placenta have CYP27B1 activity; cultured human syncytiotrophoblasts and decidual cells synthesize  $1,25(\text{OH})_2\text{D}_3$ .<sup>27</sup> 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.<sup>29</sup> 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.<sup>2,27,30</sup> The DBP has a much higher binding affinity for  $25(\text{OH})\text{D}$  than for  $1,25(\text{OH})_2\text{D}$ , and in kidney epithelial cells, DBP plays a pivotal role in conserving  $25(\text{OH})\text{D}$  by facilitating the recovery of  $25(\text{OH})\text{D}$  from the glomerular filtrate.<sup>31,32</sup>

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.<sup>2,31,33,34</sup> The PTHrP acts as a calciotropic hormone during fetal life and in lactation.<sup>35-37</sup> The exact role of circulating PTHrP in pregnancy is unknown, but its rise may stimulate renal CYP27B1 and contribute to the increase in  $1,25(\text{OH})_2\text{D}$  concentration and, indirectly, the suppression of PTH levels.<sup>27,35,37</sup> The PTHrP arises from several sources, including the breast, myometrium, decidua, amnion, and fetal parathyroids.<sup>36</sup> Several roles of PTHrP are postulated from animal studies, including fetal chondrocyte maturation, fetal calcium transfer, and stimulation of CYP27B1 activity.<sup>33,34,36</sup> 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)<sub>2</sub>D. 1,25-dihydroxyvitamin D does not readily cross the placenta, and fetal 1,25(OH)<sub>2</sub>D levels are normally lower than maternal serum levels. The low fetal concentrations of 1,25(OH)<sub>2</sub>D 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)<sub>2</sub>D concentrations double or triple in 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)<sub>2</sub>D does not appear to pass at all.<sup>2</sup> 1,25(OH)<sub>2</sub>D levels fall rapidly after pregnancy and are normal during lactation.<sup>7</sup> 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.

and may have a possible bone protection role in the mother during pregnancy.<sup>32,35-37</sup>

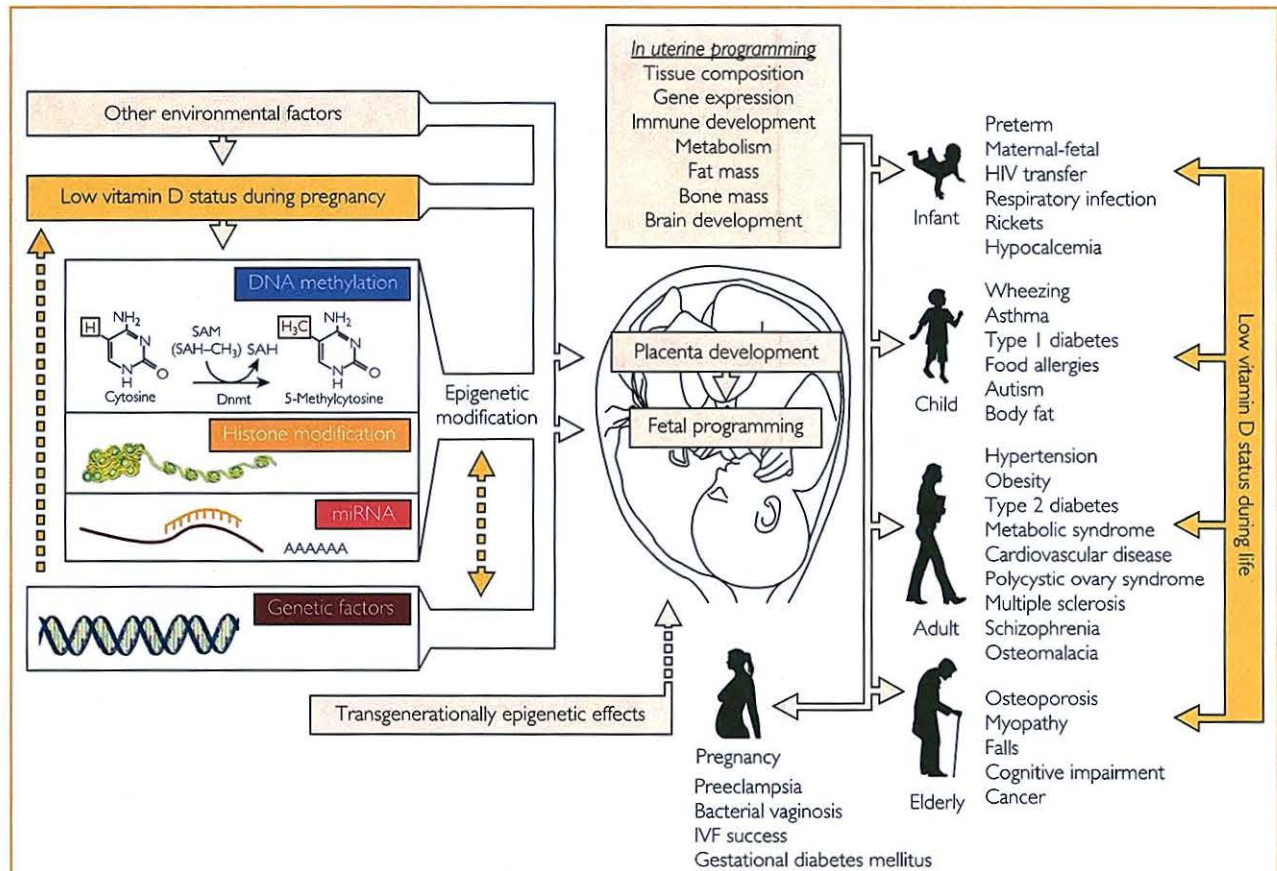
Calcitonin, an important component of calcium homeostasis during pregnancy,<sup>38,39</sup> is known to promote transcription of CYP27B1<sup>40</sup> and may, therefore, be a key determinant of placental vitamin D metabolism.<sup>41</sup> Thus, PTHrP and calcitonin, as well as other factors, cause 1,25(OH)<sub>2</sub>D levels to increase, being 2-fold higher in serum of women in the third trimester of pregnancy than in nonpregnant or postpartum women.<sup>2,27</sup> Normally, 1,25(OH)<sub>2</sub>D regulates its own metabolism via a feedback loop such that elevated concentrations induce the expression of CYP24A1, with concomitant down-regulation of CYP27B1.<sup>7,25,42</sup> This process results in a reduction of 25(OH)D and 1,25(OH)<sub>2</sub>D levels.<sup>9,29,30</sup> However, during pregnancy, this process becomes uncoupled, resulting in elevated maternal concentrations of circulating 1,25(OH)<sub>2</sub>D.<sup>27,43</sup> 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)<sub>2</sub>D bioavailability at the fetomaternal interface.<sup>44</sup>

#### 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.<sup>45-47</sup> 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.<sup>2,48</sup> The role of vitamin D in implantation tolerance and placental development has been studied. The 1,25(OH)<sub>2</sub>D<sub>3</sub> regulates key target genes associated with implantation, such as Homeobox A10 (*HOXA10*), whereas the potent immunosuppressive effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> suggest a role in placental development.<sup>49</sup> Increasing expression of CYP27B1 and VDR in first-trimester human trophoblasts and deciduas<sup>50</sup> may be related to the immunosuppressive effects of 1,25(OH)<sub>2</sub>D<sub>3</sub> 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.<sup>5,45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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.<sup>5,51</sup> 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.<sup>52</sup> This hypothesis, first articulated by Barker et al,<sup>53</sup> 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)<sub>2</sub>D bioavailability at the fetomaternal interface.<sup>25,44</sup> Modified expression of the genes encoding placental calcium transporters, by epigenetic regulation by 1,25(OH)<sub>2</sub>D, might represent the means whereby maternal vitamin D status could influence bone mineral accrual in the neonate.<sup>54,55</sup> 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).<sup>15,56</sup> Transgenerational hormonal imprinting caused by vitamin D treatment of newborn rats has been previously reported.<sup>57</sup> A recent study reported that VDR binds to the  $\epsilon$  germline gene promoter and exhibits transrepressive activity.<sup>58</sup> Inhibition



**FIGURE 3.** Vitamin D, placenta development, fetal programming, and epigenetic modification. A= adenosine; CH<sub>3</sub> = 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.

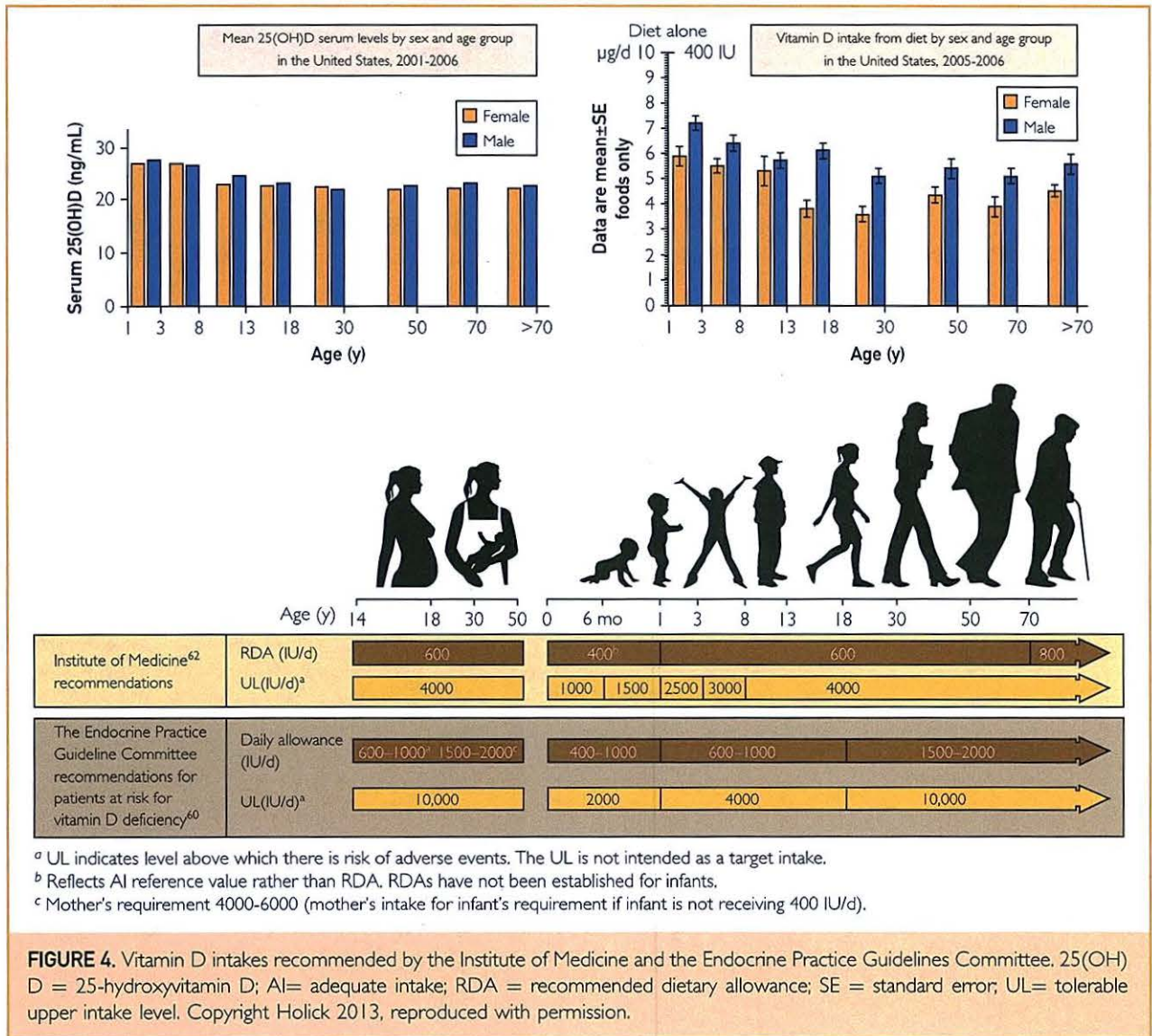
of IgE production by 1,25(OH)<sub>2</sub>D was mediated by its transrepressive activity through the VDR-corepressor complex, affecting chromatin compacting around the I $\epsilon$  region.<sup>58</sup> Also, the associations of early-life sun exposure and germline variation in VDR and CYP24A1 with non-Hodgkin lymphoma risk was reported in a clinic-based case-control study.<sup>59</sup>

#### 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)<sub>2</sub>D 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.<sup>7,15,60-63</sup> Recently, the Institute of Medicine (IOM) and the Endocrine Society released separate guidelines for vitamin D requirements.<sup>60,62</sup> 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).<sup>62</sup> 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



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.<sup>7,60</sup> 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.<sup>60</sup> 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.<sup>60</sup>

### 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.<sup>7,16,61,64-66</sup> The skeletal consequences of 25(OH)D insufficiency include secondary hyperparathyroidism, increased bone turnover and bone loss, and increased risk of low-trauma fractures.<sup>7,15,61,64</sup>

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.<sup>63,65</sup> 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.<sup>66</sup> A common early symptom in newborns is excessive sweating due to neuromuscular irritability,<sup>66</sup> 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.<sup>62,67</sup> 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.<sup>68</sup> 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.<sup>61</sup> 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.<sup>69</sup> 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.<sup>70</sup> Several RCTs have reported positive effects of vitamin D supplementation on muscle function and fall prevention.<sup>71-73</sup> Adequate calcium intake is imperative to gain optimal benefit from improving the vitamin D status in those with insufficient 25(OH)D levels.<sup>67</sup> In contrast, a study of 173 young Asian Indian females revealed that after supplementation with vitamin D<sub>3</sub> (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.<sup>74</sup> 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.<sup>7,60</sup> The relative contributions of vitamin D and calcium for reducing fracture risk remain unclear<sup>75</sup> because improving calcium intake is also associated with suppression of PTH levels independent of vitamin D status.<sup>67,76,77</sup> 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.<sup>73</sup> 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.<sup>71,73</sup> 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.<sup>78</sup> 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.<sup>78</sup> This reduction was independent of the assigned treatment dose of vitamin D, age group, sex, type of dwelling, and study.<sup>78</sup> Several previous meta-analyses have suggested that the dose of vitamin D is irrelevant when vitamin D is combined with calcium.<sup>79-82</sup> 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.<sup>78</sup>

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.<sup>83</sup> 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<sub>3</sub> and greater than 1000 mg of calcium for primary prevention of fractures in noninstitutionalized postmenopausal women.

They recommended against daily supplementation with 400 IU or less of vitamin D<sub>3</sub> 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.<sup>83</sup> 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.<sup>84</sup> 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<sup>62</sup> or at least 30 ng/mL as recommended by the Endocrine Society<sup>60</sup> 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.<sup>60-62,84-86</sup> 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)<sup>87</sup> 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.<sup>87</sup> 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.<sup>87</sup> This coincides with the recommendation from the Endocrine Society<sup>60</sup> and with the observation of Priemel et al,<sup>79</sup> 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<sup>79</sup> 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.<sup>7,60,67</sup> 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.<sup>1,2,7,19,60,61</sup>

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)<sub>2</sub>D 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
Thome-Lyman and Fawzi, <sup>88</sup> 2012	5 randomized trials 2 observational studies	28,943	Pregnant women	Vitamin D <sub>2</sub> and vitamin D <sub>3</sub> 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, <sup>89</sup> 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, <sup>78</sup> 2012	11 double-blind RCTs	31,022	Persons aged $\geq 65$ 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, <sup>90</sup> 2010	7 eligible RCTs and 17 identified case-control studies	801	Persons aged 74.8-85 y	Vitamin D <sub>2</sub> and vitamin D <sub>3</sub> (400-1100 IU)	Hip fracture risk	No effect on hip fracture risk
Bergman et al, <sup>80</sup> 2010	8 controlled trials	12,658	Postmenopausal women	Vitamin D <sub>3</sub> supplementation (800 IU/d) with or without calcium	Increasing BMD Preventing fractures	Positive effect on nonvertebral and hip fractures
Bischoff-Ferrari et al, <sup>81</sup> 2009	12 double-blind RCTs	83,165	Older individuals ( $\geq 65$ 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, <sup>82</sup> 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, <sup>75</sup> 2010	7 major randomized trials	68,517	Persons aged 47-107 y	Vitamin D <sub>2</sub> and vitamin D <sub>3</sub> (10 $\mu$ g/d to 300,000 IU/12 mo)	Antifracture efficacy	Positive effect of vitamin D with calcium on fracture No effect of vitamin D alone
Izaks, <sup>91</sup> 2007	11 trials	NA	General population	Vitamin D <sub>2</sub> and vitamin D <sub>3</sub> 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, <sup>92</sup> 2007	9 studies	2410	Postmenopausal women	Vitamin D <sub>3</sub> (excluding the potential effect of calcium supplementation)	Risk of fall and fracture	Positive effect on risk of fall in patients treated with vitamin D <sub>3</sub>
Boonen et al, <sup>93</sup> 2007	10 RCTs	54,592	Postmenopausal women and/or older men ( $\geq 50$ 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, <sup>94</sup> 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

Bischoff-Ferrari et al, <sup>84</sup> 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, <sup>85</sup> 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, <sup>86</sup> 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, <sup>95</sup> 2009	8 RCTs	2426	Older individuals	Vitamin D <sub>2</sub> and vitamin D <sub>3</sub> (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, <sup>96</sup> 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, <sup>97</sup> 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
Buttiglieri et al, <sup>98</sup> 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, <sup>99</sup> 2011	50 randomized trials	94,148	Adults; Most trials included elderly women (>70 y)	Supplemental vitamin D (vitamin D <sub>3</sub> [cholecalciferol] or vitamin D <sub>2</sub> [ergocalciferol]) or an active form of vitamin D (1 $\alpha$ -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 <sub>3</sub> on mortality Negative effect of vitamin D <sub>3</sub> combined with calcium on nephrolithiasis Negative effect on hypercalcemia

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TABLE. Continued

Reference, year	Included studies	Sample size (No.)	Participants	Dose/duration	Outcomes	Effects
Irfam et al, <sup>100</sup> 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, <sup>101</sup> 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 <sub>3</sub> 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, <sup>102</sup> 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, <sup>103</sup> 2012	17 studies	1016	Persons aged 18-97 y	Varying dosages and treatment periods	Compared the effects of vitamin D <sub>2</sub> and vitamin D <sub>3</sub> on serum 25(OH)D concentrations	Positive effect of vitamin D <sub>3</sub> compared with vitamin D <sub>2</sub> in the raising of serum 25(OH)D concentrations
Kandula et al, <sup>104</sup> 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, <sup>105</sup> 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, <sup>106</sup> 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 <sub>1c</sub> , 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, <sup>107</sup> 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, <sup>70</sup> 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, <sup>108</sup> 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

Author(s)	Study Design	NA	Adults	NA	Reduce the risk of cardiovascular events	No effect on cardiovascular disease risk
Wang et al. <sup>109</sup> 2010	18 trials	NA	Adults	NA	Reduce the risk of cardiovascular events	No effect on cardiovascular disease risk
Pittas et al. <sup>110</sup> 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 <sup>111</sup> 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. <sup>112</sup> 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
Aulier and Gandini <sup>113</sup> 2007	18 independent RCTs	57311	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).<sup>1,2,7,16,26</sup> Another vitamin D-regulated gene is CYP3A4, whose protein product detoxifies the bile acid lithocholic acid.<sup>114</sup> 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)<sub>2</sub>D could explain a protective role for improving vitamin D status against colon cancer.<sup>114</sup> 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.<sup>7,61,115-126</sup> As the importance of non-coding RNAs has emerged, the ability of 1,25(OH)<sub>2</sub>D to regulate microRNAs (miRNAs) has been found in several cancer cell lines, patient tissues, and sera. In vitamin D<sub>3</sub> intervention trials, significant differences in miRNAs were observed between treatment groups or between baseline and follow-up.<sup>116</sup> 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<sub>3</sub> intake in patients and 1,25(OH)<sub>2</sub>D<sub>3</sub> in vitro not only regulates specific miRNA(s) but also up-regulates global miRNA levels.<sup>116</sup>

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.<sup>97,114,115,117-120</sup> 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.<sup>97</sup> 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.<sup>115</sup> 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.<sup>97,121</sup> 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<sub>3</sub> 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<sub>3</sub> and calcium for 7 years and had baseline serum 25(OH)D levels greater than 24 ng/mL.<sup>84,122</sup>

Although cross-sectional data have many limitations, the findings are hypothesis generating and can be used to develop protocols for RCTs.<sup>84,123,124</sup> The findings from prospective case-control cohort studies in which blood collection occurred many years before diagnosis add another dimension to the evidence.<sup>118</sup> 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.<sup>7,97,103</sup> 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.<sup>118,125-127</sup> 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.<sup>62,123,124,128</sup> A good example is the WHI.<sup>129</sup> 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.<sup>124,129</sup> 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.<sup>7,26,61,127,128</sup> 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%.<sup>84</sup> In another RCT, a 60% reduction in all cancers was observed in postmenopausal women who ingested 1100 IU of vitamin D<sub>3</sub> and 1500 mg of elemental calcium daily for 4 years.<sup>130</sup> 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.<sup>131</sup> In a study of men and women enrolled in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial,<sup>132</sup> 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.<sup>133</sup> 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<sup>120,134,135</sup> 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.<sup>120,134-136</sup> 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.<sup>135,136</sup> 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.<sup>137</sup> 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,

kidney, or ovary.<sup>137</sup> 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.<sup>138</sup> Weaker evidence was observed for 9 other types of cancer: brain, gallbladder, laryngeal, oral/pharyngeal, prostate, and thyroid cancers; leukemia; melanoma; and myeloma.<sup>138</sup> Although there was compelling evidence for the association between vitamin D intake and cancer risk, a meta-analysis by Buttigliero et al<sup>98</sup> 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.<sup>139</sup> 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.<sup>126</sup> 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.<sup>126</sup> 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?<sup>128,140</sup> 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.<sup>141</sup> 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,<sup>126</sup> 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.<sup>142</sup> 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.<sup>143</sup> 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.<sup>144</sup> 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.<sup>145</sup> 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.<sup>146</sup> 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.<sup>146</sup> Consistent with the beneficial effect of vitamin D on risk of mortality, a meta-analysis of 50

randomized trials by Bjelakovic et al<sup>99</sup> found a positive effect of vitamin D<sub>3</sub> on mortality.

### Cardiovascular Disorders and Type 2 Diabetes Mellitus

Observational studies in humans found that 25(OH)D and 1,25(OH)<sub>2</sub>D levels are inversely related to coronary artery calcifications<sup>147,148</sup> and are lower in patients with myocardial infarction.<sup>149</sup> 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.<sup>150</sup> Additionally, 1,25(OH)<sub>2</sub>D<sub>3</sub> 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.<sup>4,151</sup> 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.<sup>150</sup> 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.<sup>4,150</sup> 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.<sup>149</sup>

Wang et al<sup>152</sup> 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.<sup>152</sup> Observational studies indicated that a serum 25(OH)D level less than 30 ng/mL was strongly associated with hypertension and metabolic syndrome.<sup>153</sup> This effect is thought to be partly mediated through regulation of the renin-angiotensin-aldosterone axis.<sup>154</sup> 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.<sup>153</sup> Black normotensive children who received 2000 IU/d of vitamin D<sub>3</sub> were compared with those who received 400 IU/d for 16 weeks in an RCT. Teenagers who received 400 IU/d of vitamin D<sub>3</sub> increased their mean  $\pm$  SD plasma levels of 25(OH)D from 13.6 $\pm$ 4.2 to 23.9 $\pm$ 7.2 ng/mL and had no reduction in arterial wall stiffness. In contrast, teenagers who received 2000 IU/d of vitamin D<sub>3</sub> increased their mean  $\pm$  SD plasma levels of 25(OH)D from 13.2 $\pm$ 3.4 to 34.2 $\pm$ 12.1 ng/mL and significantly lowered their arterial wall stiffness.<sup>155</sup> 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.<sup>156</sup> 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.<sup>156</sup>

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.<sup>157</sup> 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.<sup>158</sup> 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  $\mu$ g/d

(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.<sup>158</sup> 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.<sup>106</sup> A meta-analysis of 15 trials by George et al<sup>106</sup> 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<sup>109</sup> and Pittas et al<sup>110</sup> 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,<sup>109</sup> but most studies that used lower doses found no clinically meaningful effect.<sup>110</sup>

#### 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).<sup>159</sup> 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<sub>H</sub>) type 17 response. Because T<sub>H</sub>17 cells are critical in the pathogenesis of RA, this has led to an interest in the effects of vitamin D deficiency in RA.<sup>160</sup> Vitamin D inhibits immune reactions in general, but it enhances the transcription of endogenous antibiotics, such as cathelicidin and defensins.<sup>26,161</sup> Vitamin D suppresses autoimmune disease pathology by regulating the differentiation and activity of CD4<sup>+</sup> T cells, resulting in a more balanced T<sub>H</sub>1/T<sub>H</sub>2 response that favors less development of self-reactive T cells and autoimmunity.<sup>162</sup> The T<sub>H</sub>1-dependent autoimmune diseases, including MS, type 1 diabetes, CD, and RA, are also inhibited by 1,25(OH)<sub>2</sub>D<sub>3</sub> owing to inhibition of antigen presentation, reduced polarization of T<sub>H</sub>0 cells to T<sub>H</sub>1 cells, and reduced production of cytokines from the latter cells.<sup>161</sup> The 1,25(OH)<sub>2</sub>D<sub>3</sub> down-regulated the proinflammatory cytokine (interleukin 1 $\beta$ , 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.<sup>163</sup> 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.<sup>164</sup> 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%.<sup>164</sup> Use of a high-dose vitamin D<sub>3</sub> analogue resulted in improvement of symptoms of RA in 89% of patients, with 45% of patients entertaining a complete remission.<sup>165</sup> Recent evidence has suggested a significant inverse relationship between serum 25(OH)D levels and visual analog scale scores in patients with RA.<sup>166</sup> Very low serum 25(OH)D levels ( $\leq 6$  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.<sup>167</sup>

There is a large body of evidence linking a lack of vitamin D early in life to the development of type 1 diabetes.<sup>168</sup> Vitamin D supplementation during infancy was reported to confer partial protection against  $\beta$ -cell autoimmunity.<sup>169</sup> 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.<sup>5</sup> 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.<sup>5</sup> 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.<sup>170</sup>

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.<sup>171</sup> The 1,25(OH)<sub>2</sub>D<sub>3</sub> has been reported in animal models and in cultured cells to improve insulin production, modulate T- and  $\beta$ -cell activity, enhance phagocytic killing activity, improve vascular smooth muscle resistance, and

reduce the risk of autoimmune diseases.<sup>7,155,162</sup> 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  $\beta$ -cell function relative to insulin sensitivity.<sup>172</sup> It remains to be determined whether in youth with dysglycemia the relationships are different and whether vitamin D optimization enhances insulin sensitivity and  $\beta$ -cell function.<sup>172</sup>

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.<sup>173</sup> 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%.<sup>174</sup> 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.<sup>175</sup> Higher 25(OH)D levels were associated with decreased exacerbation risk in relapsing-remitting MS.<sup>175</sup> However, the literature is limited by small study sizes, heterogeneity of dosing, form of vitamin D tested, and clinical outcome measures.<sup>176</sup> Whether vitamin D<sub>3</sub> immunomodulatory effects can be translated into clinical benefits in patients with MS is still a matter of debate.<sup>176</sup> High doses of vitamin D<sub>3</sub> (up to 280,000 IU/wk for 6 weeks) have been used safely in patients with MS.<sup>177,178</sup> 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.<sup>177</sup> A trial using high-dose vitamin D<sub>2</sub> to achieve 25(OH)D levels of 52 to 78 ng/mL did not reduce magnetic resonance imaging lesions in relapsing-remitting MS.<sup>178</sup> In a trial using escalating doses up to 40,000 IU/d of vitamin D<sub>3</sub> 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.<sup>179</sup>

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.<sup>180</sup> In a clinical trial in patients with CD in remission, 1200 IU of vitamin D<sub>3</sub> daily increased mean  $\pm$  SD serum 25(OH)D levels from 27.6 $\pm$ 12.4 to 38.4 $\pm$ 10.8 ng/mL after 3 months.<sup>181</sup> The relapse rate was numerically lower in patients treated with vitamin D<sub>3</sub> (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<sub>3</sub> or 1,25(OH)<sub>2</sub>D<sub>3</sub> and were matured with lipopolysaccharide (LPS).<sup>182</sup> After stimulation with 25(OH)D<sub>3</sub>, 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<sub>3</sub> reduced the ability of DCs to activate lymphocytes. These data indicate that intrinsic activation of 25(OH)D<sub>3</sub> to 1,25(OH)<sub>2</sub>D<sub>3</sub> occurs in DCs from patients with CD and provides evidence that higher serum 25(OH)D<sub>3</sub> levels can potentially modulate DC function in CD.<sup>182</sup> 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.<sup>177,178,181</sup>

### 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.<sup>26,183</sup> 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*.<sup>7,26,28</sup> In turn, 25(OH)D is converted to 1,25(OH)<sub>2</sub>D, which signals the nucleus to increase the expression of cathelicidin, a defensin protein that kills infective agents, such as tuberculosis bacillus.<sup>7,26,28</sup>

Cord blood 25(OH)D levels were associated with tolerogenic immune regulation and fewer respiratory tract infections in newborns.<sup>184</sup> 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.<sup>184</sup> 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.<sup>185</sup> 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%.<sup>186</sup> 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.<sup>186</sup> 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.<sup>187</sup>

The potential role of vitamin D in reducing the risk of allergies also may be related to epigenetic regulation.<sup>188,189</sup> 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.<sup>188,190</sup> 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;  $P=.01$ ).<sup>189</sup> 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.<sup>191</sup> 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.<sup>2</sup> 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<sup>111</sup> and recovery from tuberculosis<sup>112</sup> 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)<sub>2</sub>D<sub>3</sub>. In vivo mouse studies found that in utero hypovitaminosis D impairs brain development and leads to persistent changes in the adult brain.<sup>192</sup> The 1,25(OH)<sub>2</sub>D<sub>3</sub> is rapidly incorporated into embryonic hippocampal cells, moves into the nucleus, and then returns to the cytoplasm.<sup>193</sup> 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.<sup>193</sup> At birth, rats with prenatal vitamin D deficiency had heavier and longer brains, enlarged lateral ventricles, and decreased cortical thickness.<sup>5,192,194-196</sup> 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.<sup>5,194</sup> In addition, there may be a critical window during late gestation in which vitamin D insufficiency precipitates an altered adult behavioral phenotype.<sup>195</sup> 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.<sup>196</sup> In a Finnish birth cohort study, 9114 individuals were drawn from the northern Finland 1966 birth cohort.<sup>197</sup> 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.<sup>197</sup>

There is minimal evidence for an association of low maternal vitamin D status with risk of autism.<sup>5</sup> 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.<sup>198</sup>

The 1,25(OH)<sub>2</sub>D<sub>3</sub> seems to have a neuroprotective role, inducing remyelination by endogenous progenitor cells and stimulation of amyloid- $\beta$  clearance by macrophages of patients with Alzheimer disease.<sup>199</sup> A vitamin D<sub>3</sub>-enriched diet correlated with a decrease in the number of amyloid plaques and inflammation in the brains of A $\beta$ PP mice.<sup>199</sup> These observations suggest that a vitamin D<sub>3</sub>-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.<sup>200</sup> Vitamin D deficiency was also associated with prominent changes in behavior and brain neurochemistry in the adult mouse.<sup>201</sup> 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.<sup>202</sup> 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).<sup>203</sup> In a community setting, depressed adults had significantly lower 25(OH)D levels than those without depression.<sup>204</sup> A variety of studies found an association between a low level of 25(OH)D and a high depression score.<sup>205,206</sup> 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.<sup>207,208</sup> 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.<sup>177,178</sup>

### 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).<sup>209</sup> 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.<sup>50</sup> 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.<sup>50</sup> Protein expression of *CYP2R1* and VDR were reduced, but *CYP27B1* and *CYP24A1* expressions were elevated in preeclamptic compared with normotensive placentas.<sup>50</sup> 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*.<sup>50</sup> These data indicate that fetal (trophoblastic) autocrine synthesis of 1,25(OH)<sub>2</sub>D<sub>3</sub> 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)<sub>2</sub>D<sub>3</sub> improves the angiogenic properties of endothelial progenitor cells. These findings could explain the positive influence of vitamin D<sub>3</sub> in reducing preeclampsia risk.<sup>151</sup>

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

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

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.<sup>89</sup> 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.<sup>89</sup> 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.<sup>211</sup> 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<sup>88</sup> and De-Regil et al<sup>89</sup> 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.<sup>212,213</sup> Binkley et al<sup>214</sup> 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.<sup>215</sup> 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.<sup>216</sup>

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.<sup>217,218</sup> This makes diagnostic and therapeutic decisions on the basis of absolute cutoff values for vitamin D deficiency extremely problematic<sup>219,220</sup> 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.<sup>221</sup> 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<sub>2</sub> and 25(OH)D<sub>3</sub>] 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<sub>2</sub> and 25(OH)D<sub>3</sub> levels.<sup>222</sup> The level of 25(OH)D<sub>2</sub> is underestimated by 20% to 80% and can vary for different patients who received vitamin D<sub>2</sub> 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.<sup>222</sup> 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.<sup>208</sup> Recognizing the importance of a 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub> reference material, the National Institute of Standards and Technology released a 4-level Standard Reference Material set, SRM972.<sup>221</sup> Treatment with vitamin D<sub>2</sub>, therefore, may not be accurately monitored using many of the commercial assays because these antibody assays often underestimate 25(OH)D<sub>2</sub> 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<sub>2</sub> (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.<sup>223</sup> For these patients, use of the gold standard LC-MS/MS would quantitatively report 25(OH)D<sub>2</sub>, 25(OH)D<sub>3</sub>, 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<sup>224</sup> 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).<sup>2</sup> In the United States, vitamin D deficiency and insufficiency is estimated to be 27% to 91% in pregnant women.<sup>2</sup> 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.<sup>124,128</sup>

The prevalence of vitamin D deficiency and insufficiency in children in China is high, especially in children aged 6 to 16 years.<sup>211</sup> 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.<sup>156</sup> Recent studies reported that adolescents and young adults are also at risk for vitamin D deficiency.<sup>16,128,217</sup> Also, a high prevalence of vitamin D deficiency was reported in a cross-sectional study conducted at a tertiary care center in western India.<sup>225</sup>

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.<sup>15,217</sup> This recent evidence emphasizes the high prevalence of vitamin D deficiency throughout the world, not only in at-risk groups (Figure 5).<sup>7,15,217,224-230</sup>

#### 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.<sup>228,229</sup> The prevalence of

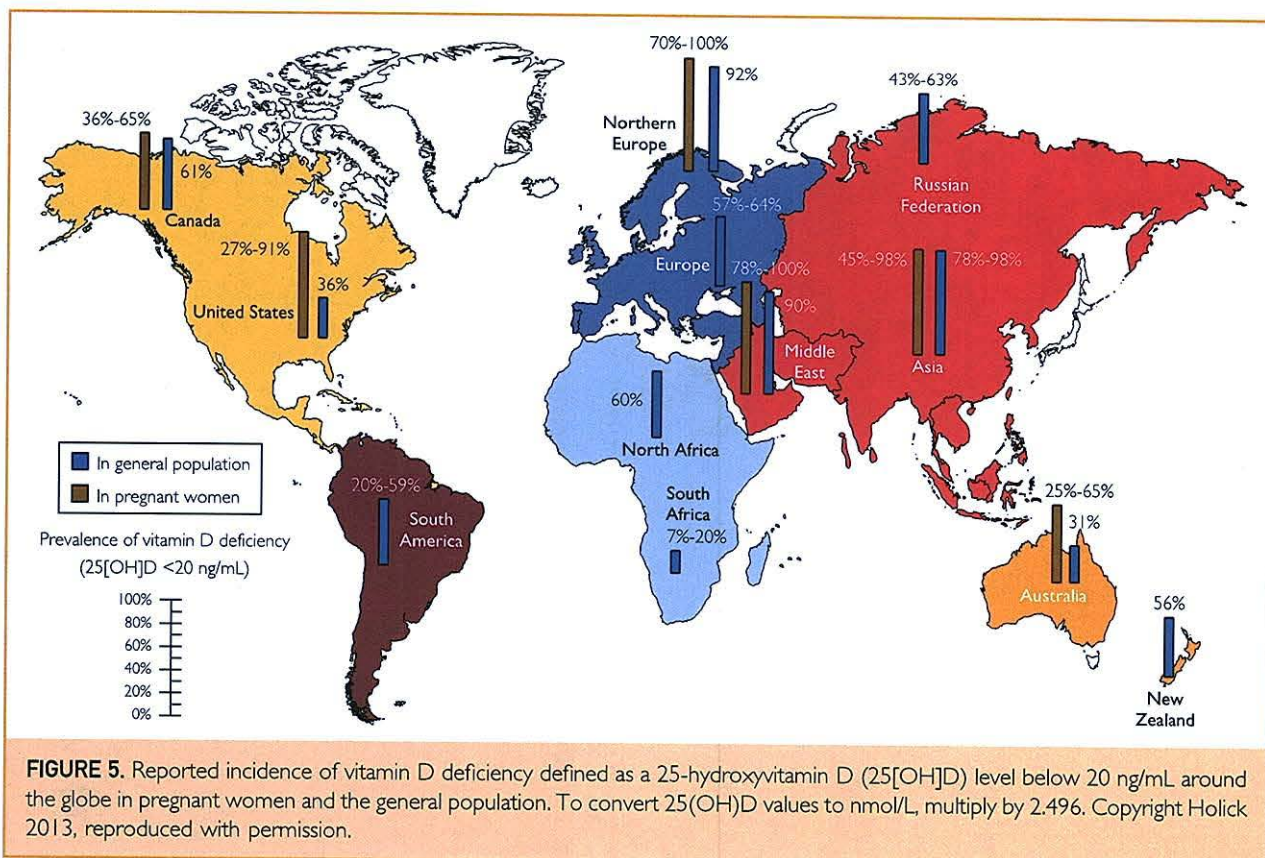
serum 25(OH)D levels less than 20 ng/mL was almost one-third of the US population (32%).<sup>217</sup> More than 70% of non-Hispanic black individuals and more than 40% of Hispanic/Mexican individuals were at risk for a 25(OH)D level less than 20 ng/mL.<sup>228</sup> In a national Canadian cohort, serum 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).<sup>229</sup> 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.<sup>230</sup> Levels of 25(OH)D were higher in northern Europe than in southern Europe and were higher in western Europe than in eastern Europe.<sup>230</sup> The higher levels in northern Europe were also observed in some multicenter studies in which a single laboratory facility was used.<sup>230</sup>

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.<sup>226</sup>

In the Middle East and Asia, vitamin D deficiency in children and adults is highly prevalent.<sup>7,227</sup> Children and adults of color are especially at high risk owing to the inefficient cutaneous production of vitamin D<sub>3</sub>.<sup>1,2,7</sup> 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.<sup>226</sup> 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.<sup>7,231</sup>

#### 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.<sup>7,228</sup> The major source of vitamin D for children and adults is exposure to natural sunlight.<sup>7,61</sup> The Maasai and



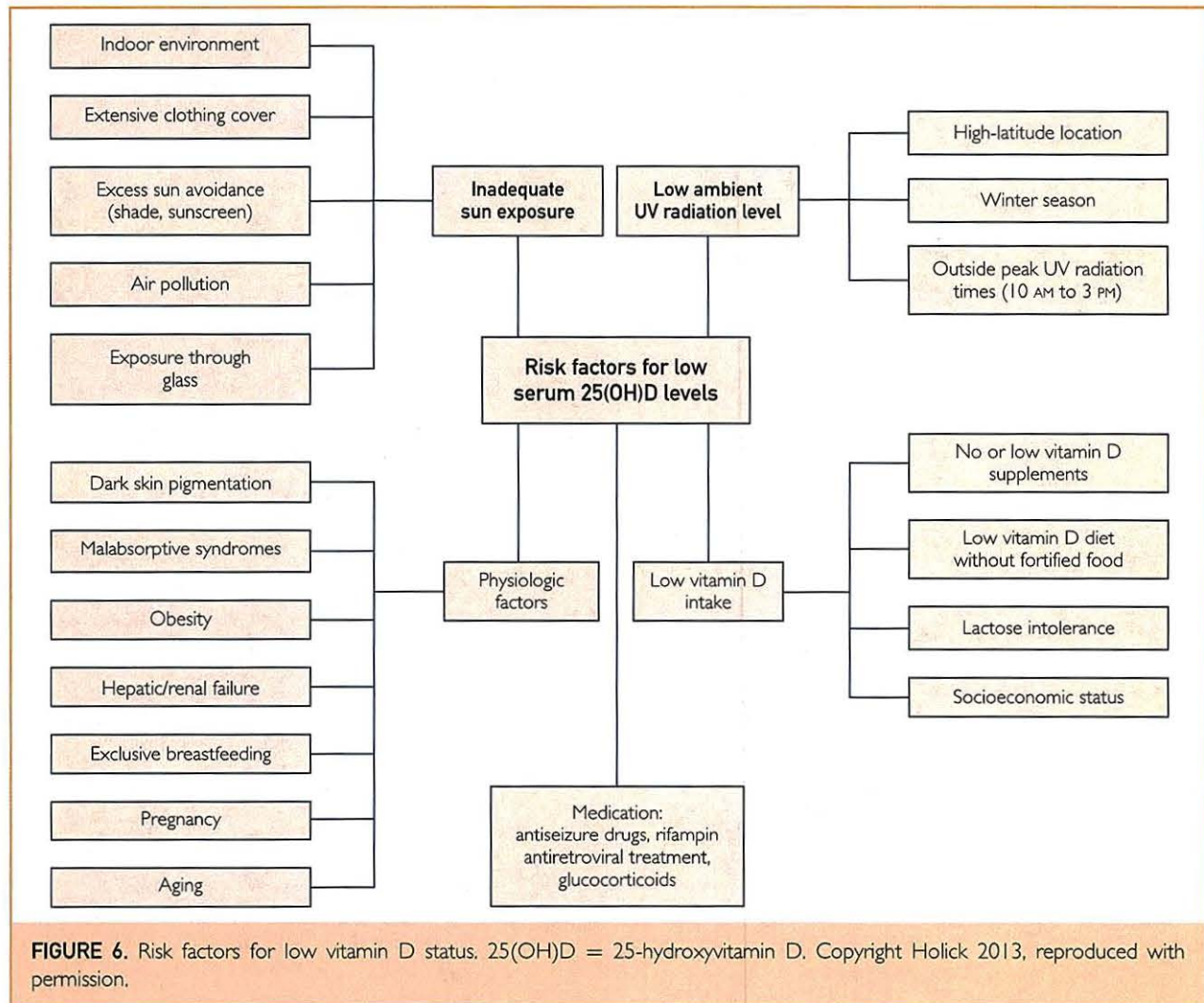
Hadzabe tribes in Tanzania (East Africa) with traditional lifestyles, living in the presumed cradle of humankind, who are exposed daily to tropical sunlight had a mean circulating 25(OH)D level of 46 ng/mL.<sup>140</sup>

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.<sup>232</sup> 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.<sup>61,233</sup> 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.<sup>234</sup> 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.<sup>235</sup>

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.<sup>236,237</sup> A comparison of the amount of previtamin D<sub>3</sub> 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<sub>3</sub>.<sup>237</sup>



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.<sup>238,239</sup> 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.<sup>239</sup> Included among these was rs2282679, a highly significant result from 2 recent genome-wide association studies (GWASs),<sup>240,241</sup> 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.<sup>241</sup> 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.<sup>242</sup> Recent epigenomic findings confirmed 3 genes (*DHCR7*,

*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.<sup>243</sup> *DHCR7* encodes the enzyme 7-DHC reductase, which converts 7-DHC to cholesterol, thereby removing the substrate from the synthetic pathway of vitamin D<sub>3</sub>.<sup>239</sup> *DHCR7* is a novel gene for association with 25(OH)D levels, as identified in 2 recent GWASs.<sup>240,241</sup> *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.<sup>240-242</sup> This mitochondrial protein initiates the degradation of 1,25(OH)<sub>2</sub>D<sub>3</sub> 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)<sub>2</sub>D.<sup>243</sup>

The genetic contributions to circulating 25(OH)D represent a complex trait for which family studies have estimated heritability ranging from 43% to 80%.<sup>244</sup> 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.<sup>244</sup> 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%).<sup>244</sup> 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)<sub>2</sub>D and can be a cause of infantile hypercalcemia.<sup>245</sup> 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.<sup>7,140</sup> 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.<sup>124,246</sup> 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.<sup>1,124,246,247</sup> Therefore, it is not unreasonable to consider sensible sun exposure as a good source of vitamin D.<sup>7,124</sup> 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<sub>2</sub> orally.<sup>7,15</sup> Thus, exposure of arms and legs to 0.5 minimal erythemal dose is equivalent to ingesting approximately 3000 IU of vitamin D<sub>3</sub>.<sup>7,60</sup> 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.<sup>248</sup> 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.<sup>249</sup> Time of day during sun exposure, season, latitude, and degree of skin pigmentation dictate how much vitamin D<sub>3</sub> 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.<sup>7</sup> 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<sub>3</sub>. A free app, [dminder.info](http://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.<sup>250</sup>

### 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.<sup>7</sup> 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.<sup>251</sup>

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.<sup>7,252</sup> 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.<sup>252</sup>

### Vitamin D Supplementation

The RDA for vitamin D and tolerable upper-limit levels vary in different age groups and in certain circumstances.<sup>7,60,62</sup> Although it is recommended that RDAs of 600 to 800 IU daily should meet the requirements to optimize bone health<sup>62</sup> 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.<sup>7,60</sup> 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.<sup>253</sup> 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.<sup>7,71</sup> An effective strategy to treat vitamin D deficiency and insufficiency in children and adults is to give them 50,000 IU of vitamin D<sub>2</sub> once a week for 6 and 8 weeks, respectively.<sup>60,254</sup> To prevent recurrence of vitamin D deficiency in children, administration of 600 to 1000 IU/d is effective.<sup>60</sup> For adults, to prevent recurrence of

vitamin D deficiency, administration of 50,000 IU of vitamin D<sub>2</sub> every 2 weeks is effective.<sup>7,60,255</sup>

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.<sup>255</sup>

Vitamin D can be administered daily, weekly, monthly, or every 4 months to sustain an adequate serum 25(OH)D concentration.<sup>7,256-258</sup> 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<sub>3</sub> increases the risk of fracture within 3 months,<sup>256</sup> but other studies have reported reduced risk of fracture.<sup>257,258</sup>

### 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.<sup>2</sup>

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.<sup>259</sup> Eighty-one percent of their newborns were vitamin D deficient.<sup>259</sup> Maternal supplementation with 2000 and 4000 IU/d of vitamin D during pregnancy improved the maternal/neonatal vitamin D status.<sup>260</sup> 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.<sup>260,261</sup>

Human breast milk and unfortified cow's milk have little vitamin D.<sup>7,260,261</sup> 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.<sup>260,261</sup>

### 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.<sup>7,60</sup> Patients taking antiepileptic medications, AIDS medications, and glucocorticoids often require more vitamin D to satisfy their requirements.<sup>7,60</sup> 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)<sub>2</sub>D produced in the macrophages in the granulomas.<sup>7</sup> Therefore, their vitamin D intake needs to be carefully monitored and controlled.<sup>7,60</sup> 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 *Spermi* lamp can be used, where available, in patients with malabsorption syndromes.<sup>250,262</sup>

### Type of Vitamin D Supplementation

Either vitamin D<sub>2</sub> or vitamin D<sub>3</sub> can be used for vitamin D supplementation, although there is controversy regarding vitamin D<sub>3</sub> vs vitamin D<sub>2</sub> for achieving and maintaining higher serum 25(OH)D levels. Although a recent meta-analysis indicated that vitamin D<sub>3</sub> is more efficacious at raising serum 25(OH)D concentrations than is vitamin D<sub>2</sub>,<sup>2,102</sup> several prospective studies have found them to be equally effective in raising and maintaining serum 25(OH)D levels in children and adults.<sup>263,264</sup> Holick et al<sup>264</sup> found that an 11-week course of treatment with 1000 IU/d of vitamin D<sub>2</sub>, 1000 IU/d of vitamin D<sub>3</sub>, or a combination of 500 IU of vitamin D<sub>2</sub> and 500 IU of vitamin D<sub>3</sub> daily caused an equivalent increase in serum total 25(OH)D levels. Furthermore, the group that received vitamin D<sub>2</sub> did not experience a significant change in serum 25(OH)D<sub>3</sub> levels. Gordon et al<sup>265</sup> and Thacher et al<sup>266</sup> also found that in infants and toddlers treated for 6 weeks, 2000 IU of vitamin D<sub>2</sub> and 2000 IU of vitamin D<sub>3</sub> daily or a single dose of 50,000 IU of vitamin D<sub>2</sub> or vitamin D<sub>3</sub> were equally effective in increasing the serum total 25(OH)D level. The

bioavailability of vitamin D<sub>3</sub> is well established, and the bioavailability of vitamin D<sub>2</sub> from mushrooms in humans has been found to be comparable with that of a vitamin D<sub>2</sub> supplement.<sup>267</sup> Finally, adults treated with vitamin D<sub>2</sub> not only raised their total blood levels of 25(OH)D but also maintained total blood levels of 1,25(OH)<sub>2</sub>D to the same degree as adults who received the same dose of vitamin D<sub>3</sub>.<sup>263</sup>

### 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.<sup>7,60,90</sup> Daily doses of vitamin D<sub>3</sub> up to 10,000 IU were safe in healthy males, and there was no evidence of hypercalcemia or hypercalciuria for 5 months.<sup>253,268</sup> 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<sub>3</sub> 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.<sup>269</sup>

### 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)<sub>2</sub>D 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<sub>3</sub> 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.<sup>17</sup> The observation that 1,25(OH)<sub>2</sub>D 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<sub>H</sub> = T helper cell; VDR = vitamin D receptor; WHI = Women's Health Initiative; 1,25(OH)<sub>2</sub>D = 1,25-dihydroxyvitamin D; 7-DHC = 7-dehydrocholesterol; 25(OH)D = 25-hydroxyvitamin D

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## **Supplementation and therapeutic use of vitamin D in patients with multiple sclerosis: Consensus of the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology**

A consensus guideline clinical recommendation from the Brazilian Academy of Neurology for treatment of Multiple Sclerosis in Arq Neuropsiquiatr 2014 by Brum et al. found: 1) all Patients should be vitamin D treated; 2) all should be above 30 ng/ml; 3) levels above 100 ng/ml should be avoided pending new guidelines; 4) monotherapy with only vitamin D is not recommended; 5) vitamin D levels above 40 show immune system improvement, so the recommendation is to maintain between 40 ng/ml and 100 ng/ml; 6) both 5,000 and 10,000 IU were safe doses to achieve 40-100 ng/ml; 7) monitoring after increasing dosage; and, 8) as a secosteroid it should be escalated dosing.

# Supplementation and therapeutic use of vitamin D in patients with multiple sclerosis: Consensus of the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology

Suplementação e uso terapêutico de vitamina D nos pacientes com esclerose múltipla: Consenso do Departamento Científico de Neuroimunologia da Academia Brasileira de Neurologia

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## ABSTRACT

Multiple sclerosis (MS) is an inflammatory, autoimmune, demyelinating, and degenerative central nervous system disease. Even though the etiology of MS has not yet been fully elucidated, there is evidence that genetic and environmental factors interact to cause the disease. Among the main environmental factors studied, those more likely associated with MS include certain viruses, smoking, and hypovitaminosis D. This review aimed to determine whether there is evidence to recommend the use of vitamin D as monotherapy or as adjunct therapy in patients with MS. We searched PUBMED, EMBASE, COCHRANNE, and LILACS databases for studies published until September 9<sup>th</sup>, 2013, using the keywords "multiple sclerosis", "vitamin D", and "clinical trial". There is no scientific evidence up to the production of this consensus for the use of vitamin D as monotherapy for MS in clinical practice.

**Keywords:** vitamin D, multiple sclerosis, experimental autoimmune encephalitis.

## RESUMO

A esclerose múltipla (EM) é uma doença inflamatória, autoimune, desmielinizante e degenerativa do sistema nervoso central. Estudos epidemiológicos têm identificado associações de hipovitaminose D com doenças autoimunes. O principal objetivo desta revisão é responder se há evidências que indiquem o uso terapêutico de vitamina D em monoterapia para pacientes com EM. Por meio dos sites PUBMED, EMBASE, LILACS e Scielo foram realizadas buscas usando os descritores "vitamin D", e "multiple sclerosis" até 12/09/2013. Estudos clínicos randomizados, controlados e duplo-cegos foram selecionados para avaliar a resposta terapêutica da vitamina D na EM. Não foram encontradas evidências científicas que justifiquem o uso da vitamina D em monoterapia no tratamento da EM, na prática clínica.

**Palavras-chave:** Vitamina D, esclerose múltipla, encefalite autoimune experimental.

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**Conflict of interest:** The Brazilian Academy of Neurology (ABN) is committed to produce clinical guidelines critically and independently. This guideline is part of ABN's continuing education activity. It is based on review of scientific and clinical knowledge. Its purpose is not to address the subject in its entirety. Treatment decision is shared between patient and physician and according to each situation.

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The therapeutic use of vitamin D for treating multiple sclerosis (MS) is a controversial issue that is of interest to physicians, researchers, and patients. The Scientific Department of Neuroimmunology (DCNI) of the Brazilian Academy of Neurology (ABN) organized a meeting on September 12, 2013, to discuss the basic aspects of vitamin D metabolism, results of *in vitro* and experimental studies on experimental autoimmune encephalomyelitis (EAE), and controlled clinical trials of vitamin D in MS. Neurologists and researchers participating in the meeting approved a guideline consensus to guide Brazilian neurologists in the care of patients with MS.

## VITAMIN D, MS, AND EAE

Vitamin D is an important hormone for calcium homeostasis and bone metabolism<sup>1</sup>. Besides its action in bone tissue, vitamin D has a role in cell differentiation, cell growth inhibition, and immune system modulation<sup>2</sup>. The main source of vitamin D is ultraviolet-B radiation (95%). However, no consensus has been reached on optimal serum vitamin D levels for human metabolic needs<sup>3,4</sup>. The association between vitamin D and autoimmune diseases and neoplasms has been established in recent years<sup>5</sup>, but this relationship has not yet been fully elucidated.

Multiple sclerosis is an inflammatory, autoimmune, demyelinating, and degenerative central nervous system (CNS) disease, whose geographic and ethnic distribution is characterized by a higher prevalence in northern hemisphere countries, particularly in populations of Caucasian origin<sup>6</sup>.

The predominantly temperate climate in the northern hemisphere with long periods of low solar radiation and the relatively high prevalence of hypovitaminosis D observed in population studies<sup>7</sup> have led to the hypothesis that this deficiency may explain the geographical distribution of MS. Moreover, it has been suggested that adequate serum levels of vitamin D could help reduce the risk of developing MS<sup>8,9</sup>.

Even though the etiology of MS has not yet been fully elucidated, there is evidence that genetic<sup>10,11</sup> and environmental<sup>12</sup> factors interact to cause the disease. Among the main environmental factors studied, those more likely associated with MS include certain viruses<sup>13</sup>, smoking<sup>14</sup>, and hypovitaminosis D<sup>15,16</sup>. The latter is particularly important in the northern hemisphere, where the seasonal variation and subsequent reduction in ultraviolet-B radiation in winter may lead to a higher prevalence of hypovitaminosis D. Some conditions represent risk of hypovitaminosis D in the general population such as long stay indoors, use of sunscreen, and skin pigmentation<sup>17,18</sup>. Motor limitations associated with later stages of MS may contribute to the occurrence of hypovitaminosis D in this group of patients<sup>19</sup>.

Unlike northern hemisphere countries, solar radiation in Brazil is believed to be plentiful in all seasons and regions to

prevent hypovitaminosis D. Thus, the amount of sunlight one is exposed in Brazil should be enough to avoid hypovitaminosis D in healthy individuals when exposed to sunlight even for short periods. Nevertheless, no studies have compared serum vitamin D levels among Brazilian regions, whereas few studies have analyzed serum vitamin D levels in a selected risk group<sup>20</sup>.

Preliminary experimental studies have demonstrated an immunomodulatory role of vitamin D on human immune cells *in vitro*<sup>21,22</sup> and in an experimental animal model (EAE)<sup>23,24</sup>. An *in vitro* study with peripheral blood cells of patients on vitamin D therapy showed that serum levels above 40 ng/ml may exert modulatory action on immune cells<sup>20</sup>. Additional studies are underway to better understand this immunomodulatory effect on autoimmune diseases.

This review aimed to determine whether there is evidence to recommend the use of vitamin D as monotherapy or as adjunct therapy in patients with MS. We searched PUBMED, EMBASE, COCHRANNE, and LILACS databases for studies published until September 9<sup>th</sup>, 2013, using the keywords "multiple sclerosis", "vitamin D", and "clinical trial". Randomized controlled clinical trials with vitamin D in patients with MS were included in the analysis.

## RANDOMIZED AND CONTROLLED CLINICAL TRIALS WITH VITAMIN D IN THE TREATMENT OF MS

To evaluate the therapeutic response of vitamin D in MS patients, we selected double-blind, randomized, controlled clinical trials from the literature<sup>25,26-28</sup>. These studies are still scarce and most were not designed to evaluate therapeutic response to vitamin D. Next, we discuss the most relevant studies.

A clinical study conducted in Finland<sup>25</sup> in 66 patients with relapsing-remitting multiple sclerosis (RRMS) compared a group with 34 patients using 20,000 IU/week of vitamin D and interferon beta-1b (IFN $\beta$ -1b) to another group with 32 patients using IFN $\beta$ -1b only. In that study, primary outcomes included tolerability and safety aspects, and number of new lesions and gadolinium enhancing lesions on MRI scans. Secondary outcomes included clinical parameters such as annual relapse rate and changes in the Expanded Disability Scale Score (EDSS), in addition to other imaging parameters. The authors observed that the treated group showed fewer new T2 lesions, but there were no significant differences in clinical parameters between the two groups after 12 months. However, there was a significant reduction in the number of gadolinium enhancing lesions in the vitamin D group.

Another study, conducted in Norway<sup>26</sup>, compared bone mineral density, relapse frequency, disease progression, and motor function measures between 35 patients with MS using 20,000 IU of cholecalciferol per week associated with 500

mg/day of calcium and a control group of 33 patients with MS using 500 mg/day of calcium only for two years<sup>26</sup>. Patients in both groups had been previously using immunomodulatory drugs (interferon beta or glatiramer acetate) for a similar period of time. No differences in annual relapse rate and changes in functional capacity measured by EDSS were observed between the two groups, even though vitamin D levels ranged from 24.72 ng/ml in the placebo group to 49.26 ng/ml in the vitamin D group. The study was not powered to address clinical outcomes<sup>12</sup>.

A phase II study developed in Iran<sup>27</sup> compared 25 patients with RRMS receiving the active form of vitamin D (calcitriol) at a dose of 0.25 µg/day with patients receiving placebo<sup>27</sup>. Both groups used conventional immunomodulators. There was no difference in the EDSS between the calcitriol and placebo groups after 12 months followup<sup>13</sup>. It should be noted in that study the small sample size and inclusion criterion of serum 25-hydroxyvitamin D level >40 ng/ml.

A randomized study in Australia<sup>28</sup> compared 11 patients with RRMS treated with vitamin D2 in a dose of 6,000 IU twice daily in addition to a daily low-dose (1,000 IU) with 12 patients receiving the 1,000 IU/day dose only<sup>28</sup>. The neuraxial index of inflammatory activity on MRI was compared between the high-dose and low-dose groups. No significant differences between the groups were detected.

A meta-analysis of the studies cited above detected no difference in the number of relapses between the groups<sup>29</sup>. The number of new lesions and gadolinium enhancing lesions were compared to serum vitamin D levels in other two studies and the findings were conflicting<sup>26,30</sup>. Limitations of the studies include different dosages and forms of vitamin D administered.

In contrast to epidemiological and experimental studies, randomized trials on the use of vitamin D in MS showed no significant differences in the parameters of disease activity – relapse rate, EDSS progression, and new or gadolinium enhancing lesions on MRI – between the group receiving vitamin D and groups receiving placebo or a smaller dose of vitamin D. These differences and other contradictions indicate the need to conduct double-blind, randomized, controlled trials in large groups of patients, considering the differences between clinical, neuroimaging, biological, and immunological variables, and powered to accurately estimate the therapeutic efficacy and possible side effects of vitamin D in MS.

## VITAMIN D AND OTHER ISSUES

### Normal range

The Institute of Medicine (IOM) and the American Society for Endocrinology advocate different levels of vitamin D to maintain bone health: ≥20 ng/ml and ≥30ng/ml,

respectively<sup>3,4</sup>. There is no consensus on whether bone cells and immune cells require different levels of vitamin D. In addition to the lack of consensus on the normal range values for vitamin D, the toxic serum concentration and the concentration leading up to this condition are also controversial. In adults, doses greater than or equal to 10,000 IU/day are associated with hypercalcemia<sup>31,32</sup>.

High performance liquid chromatography (HPLC) followed by mass spectrometry is considered the gold standard for analysis of serum 25-OH vitamin D levels. However, the technique is laborious, expensive, and is not available in most Brazilian laboratories. Other methods such as chemiluminescence, enzyme immunoassay, and radioimmunoassay are also used. Thus, variability in results can occur depending on the assay used<sup>33</sup>. In Brazil, there is no efficient inter-laboratory validation system, which can also result in great variability in results. Moreover, certain medications such as anti-convulsants and corticosteroids may have a role in reducing serum levels of vitamin D.

## SAFETY PROFILE

The safety profile of different serum vitamin D levels has been evaluated in an open, randomized study conducted in Canada<sup>31</sup>. In that study, a group of 25 patients with MS used escalating cholecalciferol (vitamin D3) doses up to 40,000 IU/day, whereas a second group of 24 patients used 4,000 IU/day. Patients in both groups used immunomodulators (interferon beta and glatiramer acetate) in combination with cholecalciferol. The maximum 40,000 IU/day dose was used for up to six months, followed by 10,000 IU/day for three months and gradual suspension over three months. Both groups received calcium (1,200 mg/day) throughout the trial, and serum calcium was determined. Serum 25-hydroxyvitamin D (25-OH-vitamin D) reached a maximum mean above 250 nmol/l (100ng/ml) during the 40,000 IU/day dosing period. No hypercalcemia was detected during the 10,000 IU/day dosing period, even with serum levels ≥ 100 ng/ml, suggesting that that dose is safe (Class level II evidence). In addition, neither serum calcium nor parathormone urinary levels were altered, even when serum concentrations were higher. Further studies are needed to confirm these findings.

## VITAMIN D – SIDE EFFECTS

Clinical picture of vitamin D intoxication may include signs and symptoms originating in different systems: nausea and vomiting, anorexia, abdominal pain, constipation; polydipsia, polyuria, dehydration, nephrolithiasis, nephrocalcinosis, nephrogenic diabetes insipidus, chronic interstitial nephritis, acute and chronic renal failure; hypotonia,

paresthesia, confusion, seizures, apathy, coma; arrhythmia, bradycardia, hypertension, cardiomyopathy; muscle weakness, calcification, osteoporosis; and conjunctival calcification<sup>34-36</sup>. Hypercalcemia is the most important side effect, and when observed in the laboratory is suggestive of intoxication<sup>37</sup>.

During use of vitamin D, in addition to serum calcium, urinary calcium should be assayed periodically. Serum concentration of parathyroid hormone (PTH) should also be determined and must not exceed the lower reference values of normality indicative of suppression, which is a non-recommended condition<sup>35</sup>.

## FINAL CONSIDERATIONS

Considering the body of information presented here, the DCNI/ABN defines the consensus that:

1. It is recommended to dose vitamin D in patients with clinically isolated syndrome and MS, regardless of the stage of disease, particularly those making frequent use of corticosteroids or anticonvulsants.
2. Peripheral blood levels of vitamin D lower than 30ng/ml should be corrected in patients with MS, at any stage, or in patients with demyelinating isolated syndrome (grade D recommendation).
3. Peripheral blood levels of vitamin D higher than 100 ng/ml should be avoided until new guidelines are established (grade D recommendation).
4. **There is no scientific evidence up to the production of this consensus for the use of vitamin D as monotherapy for MS in clinical practice.** Therefore, currently, vitamin D monotherapy for MS is considered experimental. For its use in clinical trials, these must be approved by the Human Research Ethics Committee, regulated by the National Commission for Ethics in Research (CONEP), approved by the Regional Medical Board, and informed consent should be provided by patients.
5. According to data from *in vitro* studies with peripheral blood cells of patients using vitamin D, serum levels

above 40 ng/ml are likely to cause modulating action on immune cells<sup>17</sup>. Based on that evidence, vitamin D supplementation at doses that maintain serum levels of patients between 40 ng/ml and 100 ng/ml may be recommended, as these are safe levels (grade D recommendation).

6. Considering the individual differences in replacement needs and serum levels of vitamin D, that a study in healthy subjects showed that 5,000 IU/day of vitamin D for 15 weeks increased serum levels up to 60ng/ml, and that doses up to 10,000 IU/day were considered safe, we recommend individualized doses until reaching serum levels between 40 ng/ml and 100 ng/ml (grade D recommendation).
7. Considering that low vitamin D serum levels in patients with isolated demyelinating syndrome could affect the relative risk of conversion to MS<sup>16</sup>, we recommend the analysis of serum vitamin D levels in those patients and that a correction is made whenever necessary (grade D recommendation).
8. Because vitamin D3 is a secosteroid hormone, its use should be escalated. Moreover, monitoring serum 25-hydroxvitamin D would be extremely important before increasing dosage to determine whether supplementation is actually effective (grade D recommendation).

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