The Case for Vitamin D Supplementation:
Summary of the Evidence and Recommendations

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Objectives:

• Review the 2018 vitamin D news
• Review vitamin D basics
• Survey the evidence for supplementation
• Consider some possible reasons for the recent negative studies
'No evidence' that vitamin D prevents cancer or heart attacks

Using vitamin D supplements ‘does not prevent fractures or falls’

Millions of Americans take vitamin D. Most should just stop.

Study casts doubt on vitamin D supplements
Vitamin D, the Sunshine Supplement, Has Shadowy Money Behind It

The doctor most responsible for creating a billion-dollar juggernaut has received hundreds of thousands of dollars from the vitamin D industry.
What is a “normal” level of vitamin D?

- IOM/ NAM in 2010 said > or = to 20 ng/ml

<table>
<thead>
<tr>
<th></th>
<th>Conventional Units (ng/mL)</th>
<th>SI Units (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;20</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Normal</td>
<td>≥20</td>
<td>≥50</td>
</tr>
<tr>
<td>Excessive</td>
<td>&gt;50</td>
<td>&gt;125</td>
</tr>
</tbody>
</table>

1
The Vitamin D Task Force of the Endocrine Society concluded that \( \geq 30 \text{ ng/ml} \) was sufficient.²

<table>
<thead>
<tr>
<th>Status</th>
<th>Conventional Units (ng/mL)</th>
<th>SI Units (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>&lt;20</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Insufficient</td>
<td>20–29.9</td>
<td>50–74.9</td>
</tr>
<tr>
<td>Sufficient</td>
<td>30</td>
<td>&gt;75</td>
</tr>
</tbody>
</table>
NHANES data: US 25-Hydroxyvitamin D levels (age 12 and up)⁴

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>&lt;12 ng/ml</td>
<td>5.2 (3.8, 6.9)</td>
<td>6.4 (4.8, 8.6)</td>
<td>6.7 (5.2, 8.7)</td>
</tr>
<tr>
<td>&lt;16 ng/ml</td>
<td>18 (14, 22)</td>
<td>14 (11, 18)</td>
<td>15 (12, 18)</td>
</tr>
<tr>
<td>&lt;20 ng/ml</td>
<td>32 (27, 37)</td>
<td>26 (22, 30)</td>
<td>26 (22, 30)</td>
</tr>
<tr>
<td>&lt;30 ng/ml</td>
<td>77 (73, 80)</td>
<td>65 (62, 68)</td>
<td>64 (60, 68)</td>
</tr>
</tbody>
</table>
Implications:

• Defining a 25-hydroxyvitamin D level of less than 30 ng/ml as “deficient” defined 64% of Americans as deficient in vitamin D
Accusation of commercial bias:

• Kaiser Health investigated Michael Holick PhD, MD, who helped author the Endocrine Society’s recommendation

• Identified potential conflicts of interest:
  – Quest diagnostics
  – Sanofi Adventis, Shire, Amgen
  – Roche Diagnostic, Quidel Corporation
  – UV Foundation
So what do we know?

- Traditionally living people tend to have 25 OH vitamin D levels around 45 ng/ml.
- Serum PTH levels tend to rise at 25 OH vitamin D levels below about 30 ng/ml.
Determinants of vitamin D status

• ~80% of our vitamin D is from UVB radiation from the sun hitting our skin, converting 7-dehydrocholesterol into vitamin D$_3^5$

• Remainder comes from ingestion of D$_2$ and D$_3$ in foods or supplements
Sources of vitamin D

- Sunlight
- Fortified foods
- Supplements
- Foods natural containing vitamin D
- Artificial UVB
Vitamin D is found in foods in the natural state as well as in some fortified foods. The natural sources tend to be high in fat and eaten only occasionally by most people.

<table>
<thead>
<tr>
<th>Vitamin D Sources from Foods</th>
<th>IU</th>
<th>per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eel</td>
<td>792</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Trout</td>
<td>645</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Salmon (smoked chinook)</td>
<td>583</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Swordfish</td>
<td>566</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Salmon (pink, canned)</td>
<td>465</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Salmon, sockeye</td>
<td>447</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Catfish (wild)</td>
<td>425</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Mackerel (Atlantic)</td>
<td>388</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Salmon (wild)</td>
<td>307</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Tuna (light, canned in oil)</td>
<td>229</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Sardines (Atlantic, canned in oil)</td>
<td>164</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Rockfish</td>
<td>156</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Tuna (light, canned in water)</td>
<td>154</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Halibut</td>
<td>196</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Flounder or sole</td>
<td>118</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Herring (pickled)</td>
<td>96</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Tuna (white, canned in water)</td>
<td>68</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Tuna, yellowfin</td>
<td>70</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Shiitake mushrooms</td>
<td>41</td>
<td>1 cup</td>
</tr>
<tr>
<td>Egg</td>
<td>41</td>
<td>1 large egg (including yolk)</td>
</tr>
</tbody>
</table>

Cod liver oil contains 450 IU of vitamin D per teaspoon and liver contains 42 IU per slice but they are not recommended sources of vitamin D (See Vitamin A: Get It From Colorful Fruits and Vegetables).
### Vitamin D Fortified Foods

<table>
<thead>
<tr>
<th>Fortified Sources of Vitamin D:</th>
<th>IU</th>
<th>per serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malted milk*</td>
<td>326</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Oatmeal*</td>
<td>150</td>
<td>1 packet</td>
</tr>
<tr>
<td>Milkshake</td>
<td>123 to 150</td>
<td>11 ounces</td>
</tr>
<tr>
<td>Eggnog</td>
<td>123</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Milk</td>
<td>115 to 124</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Milk (evaporated)</td>
<td>100</td>
<td>4 ounces</td>
</tr>
<tr>
<td>Milk (instant, dry)</td>
<td>100</td>
<td>½ cup</td>
</tr>
<tr>
<td>Rice drink*</td>
<td>100</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Soy milk or almond milk*</td>
<td>100</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Orange juice*</td>
<td>100</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Infant formulas</td>
<td>100</td>
<td>8 ounces</td>
</tr>
<tr>
<td>Yogurt*</td>
<td>80 to 200</td>
<td>6 ounces</td>
</tr>
<tr>
<td>Tofu*</td>
<td>80</td>
<td>3 ounces</td>
</tr>
<tr>
<td>Creamed soup made with milk</td>
<td>62</td>
<td>1 cup</td>
</tr>
<tr>
<td>Cereal, fortified</td>
<td>50 to 100</td>
<td>as listed</td>
</tr>
<tr>
<td>Pudding, made with milk</td>
<td>49 to 60</td>
<td>½ cup</td>
</tr>
<tr>
<td>Cheese*</td>
<td>40</td>
<td>1 slice or</td>
</tr>
<tr>
<td>Egg substitutes</td>
<td>50</td>
<td>¼ cup</td>
</tr>
<tr>
<td>Margarine*</td>
<td>25</td>
<td>teaspoon</td>
</tr>
</tbody>
</table>

Fortified foods (foods with vitamin D added) supply most of the vitamin D in typical U.S. diets.

*Not all brands are fortified with vitamin D. Be sure to read food labels to select brands with vitamin D added.
Vitamin D2 and vitamin D3 are not bioequivalent

- Vitamin D3 raises 25-hydroxyvitamin D levels better than equivalent doses of vitamin D2.
Factors in amount of UVB:

- Latitude
- Amount of time outdoors
- Timing of time outdoors
- Amount of exposed skin
- Air pollution
- Natural skin pigmentation
- Sunscreen use
Fitzpatrick skin types
Other factors affecting vitamin D status

- Genetics
- Age
- Body mass index
- Diet
- Supplement use
Short term factors affecting vitamin D levels:

• Seasonal variation
• Recent exposure
• Epigenetics
• Inflammation (may decrease levels)
• Lab error
Current intake recommendations:

- NIH/ NAS:
  - 400 IU per day age 0-1 year
  - 600 IU per day age 1-70 years
  - 800 IU per day age > 70 years
- EU also set adequate dose at 600 IU/ day
- Many have questioned if this is enough for everyone.
Populations at risk for deficiency

- Premature infants
- Breastfed infants
- Adolescents
- Pregnant women
- Elderly individuals
- Darker skinned immigrants
- Those who cover for religious reasons
- Institutionalized individuals
- Vegans
- Those with intestinal malabsorption
Should we check 25-hydroxyvitamin D levels?

- Yes, if we think there are adverse effects of deficiency (we’ll get to that)
- No, if we think adequate supplementation will provide adequate D to all.
Recommendation on testing:

• US Preventative Services Task Force:
  – In community-dwelling, nonpregnant, asymptomatic adults age 18 and older: Current evidence is insufficient to assess the benefits and harms of screening for vitamin D deficiency
If you do check levels, know this...

25-Hydroxyvitamin D measurement can be imprecise!
Commonly used lab methods:

– High pressure liquid chromatography and mass spectrometry (HPLC and MS)
– Radioimmunoassays (RIA)
– Chemiluminescent immunoassays (CLIA)
Precision of these tests:

Table 3

Sample coefficient of variation (SCV) values with 95% confidence intervals.

<table>
<thead>
<tr>
<th>Variable</th>
<th>SCV% (95% CI)</th>
<th>P-value</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC-APCI-MS</td>
<td>32.3 (28.5–36.0)</td>
<td>ref</td>
<td>NA</td>
</tr>
<tr>
<td>RIA</td>
<td>34.2 (29.8–38.3)</td>
<td>0.243</td>
<td>ref</td>
</tr>
<tr>
<td>CLIA</td>
<td>43.5 (37.7–48.9)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Adjusted for twin-ship dependence.
Comparison of these 3 techniques:
Percent of population labeled deficient by lab technique:

Equivalent to 20 ng/mol
Which test does M-lab use?

- Uses CLIA

- Stated reference ranges:
  - Optimal 25-100 ng/ml
  - Deficiency <10 ng/ml
  - Toxicity >150 ng/ml
Role of vitamin D

- Promotes absorption of calcium in the intestine.
- Maintains adequate serum calcium and phosphate levels to enable normal bone mineralization.
- Vitamin D deficiency causes rickets and osteomalacia.
Other roles:

- Vitamin D receptors in almost all cell types.
- It also:
  - Modulates cell growth
  - Enhances neuromuscular and immune function
  - Reduces inflammation
Proposed benefits:

• Prevention of cardiovascular disease

• Prevention of hypertension

• Reduction of insulin resistance/ type 2 DM prevention
Proposed benefits:

• Cancer prevention
  – Breast, colorectal, prostate

• Prevention of autoimmune diseases
  – MS
  – IBD
  – Type 1 DM
  – RA
  – SLE
Proposed benefits

• Neuropsychological functioning
  – Autism
  – Depression
  – Cognitive function

• Reduction of migraines
Proposed benefits:

• Improvement of asthma
• Improvement of eczema
• Improved immune response to:
  – Tuberculosis
  – Influenza
Taking vitamin D supplements may not improve bone health
“Effects of vitamin D on musculoskeletal health”

- Huge meta-analysis
- 82 RCTs
- 53,537 total participants

Bolland, BMJ 10/2018
Findings:

• RR of any fracture 1.00 (95% CI 0.93-1.07)
• RR of hip fracture 1.11 (95% CI 0.97-1.26)
• RR of falls 0.97 (95% CI 0.93-1.02)
Subgroup analysis included:

- vitamin D dose < and > 800 IU
- Daily vs intermittent dosing
- Starting 25 OH vitamin D levels
- Age
- BMI
- Other interventions (e.g. calcium, exercise)
- Community vs residential living
• **Still** no significant improvement in:
  – fractures
  – falls
  – BMD by DEXA

• Possible weakness in the study... just 6% of participants started with a vitamin D level <12.5 ng/ml
Take away?

• Based on this large meta-analysis: vitamin D supplementation should not be recommended for bone health.
So, what about those other possible benefits?
Potential confounder:

• Many of the original trials suggesting these benefits were observational, however...

  sun exposure may be a marker for activity and therefore, wellness.
Cardiovascular outcomes and cancer incidence
VITAL Trial

• “Vitamin D Supplements and the Prevention of Cancer and Cardiovascular Disease”
  – Nationwide sample
  – 25,871 participants
  – Randomized, placebo-controlled
  – Men 50 and older, women 55 and older
  – Median follow up of 5.3 years

Dawson-Hughes 3/2005
• Vitamin D2,000 IU per day +/- omega 3 fatty acids 1,000 mg per day vs placebo

• Results:
  – No statistically significant difference in end points for those getting vitamin D for:
    – Major cardiovascular events
    – Death from cancer

Dawson-Hughes 3/2005
• HR for major CV event, 0.97 (95% CI, 0.79-1.31)
• HR for death from cancer, 0.83 (95% CI, 0.67-1.02)
• HR for breast cancer 1.02 (95% CI, 0.79-1.31)
• HR for prostate cancer 0.88 (95% CI, 0.72-1.07)
• HR for colorectal cancer, 1.09 (95% CI 0.73-1.62)
• HR for death from any cause was 0.99 (95% CI 0.87-1.12)
Cancer
“Vitamin D supplementation for prevention of cancer in adults”

- 18 trials, 50,623 participants
- 80% female
- Mean age 69 (range 47-97)
- Supplementation 5 months-7 years
- Follow up 5 months to 7 years
- Vitamin D dose mean was 1146IU/ day ( ranged 333-3333 IU/day)
• RR of cancer 1.00 (95% CI 0.94-1.06)
• RR of all cause mortality 0.93 (95% CI 0.88-0.98, P 0.009)
• RR of cancer mortality 0.88 (95% CI 0.78-0.98, P 0.02)
• RR of nephrolithiasis when vitamin D combined with calcium 1.17 (95% CI 1.03-1.34, P=0.02)
All cause mortality
“Vitamin D supplementation for prevention of mortality in adults”\textsuperscript{11}

- Cochrane meta-analysis, 1/2018
- 56 studies
- 95,286 participants
- Randomized trials, not all w/ placebo
- 77% women
• Age range 18-107 years
• Mean treatment duration 4.4 years
• Mean daily dose 3,650 IU/day
• Median daily dose 800 IU/d
• Vitamin D₃ (not D₂) decreased all cause mortality RR 0.94 (95% CI 0.91-0.98, P 0.002)
Other specific benefits
“The Effect of Improved Serum 25-Hydroxyvitamin D Status on Glycemic Control in Diabetic Patients”

- 24 controlled trials
- 1528 diabetic participants
- Mean dose of vitamin D was 4074 IU/d
- Reduction in A1C by 0.30 (95% CI -0.15 to -0.45, P 0.001)
- FPG -4.9 (95% CI -8.1 to -1.6, P 0.003)
“Vitamin D supplementation for women during pregnancy”

- Cochrane review, 1/2016
- 15 trials, 2833 pregnant women
- RR of preeclampsia 0.52 (95% CI 0.25-1.05)
- RR of preterm birth 0.36 (95% CI 0.14-0.95)
- RR of low birth weight 0.40 (95% CI 0.24-0.67)
Other positive studies:

• Literature search of meta-analyses showed potential benefit to
  
  – Asthma control
  – Acute respiratory infections
  – Tuberculosis progression
Negative meta-analyses:

• No apparent benefit for:
  – Multiple sclerosis
  – Chronic pain
  – Sickle cell
The Role of Vitamin K2

• Several studies (mostly from Japan) showed a synergistic effect of vitamin K2 with vitamin D.

• BMD improvements seen when K2 added to vitamin D.

• 2 studies showed cardiovascular improvements when K2 added to vitamin D supplementation.
Take home points:

- Vitamin D supplementation alone does not improve bone or cardiovascular health
- Commercial bias should give caution to interpretation of study results
- Vitamin D in reasonable doses (up to 4000 IU/d) appears safe
- Other potential benefits of vitamin D supplementation warrant more study
- Stay alert to studies looking at the combination of vitamin D and vitamin K2
References


More references


8. NIH Vitamin D Fact Sheet for Health Professionals. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/


