Vitamin D and Health: Bones and Beyond

An Update on Current Research and Recommendations

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Vitamin D Physiology

Ultraviolet-B rays convert a derivative of cholesterol – already present in the skin – into vitamin D₃, which then travels to the liver.

The liver converts vitamin D₃ to another form called 25-hydroxyvitamin D [25(OH)D] which is measured to assess vitamin D status.

The kidneys convert this form to the final active hormone [1,25-dihydroxyvitamin D] that may have many effects throughout the body.

Many other tissues and organs express VDRs, and the enzyme 25OHD-1α hydroxylase (CYP27B1) which converts 25(OH)D into 1,25(OH)D.
Non-Skeletal Effects of Vitamin D

Biologic effects of vitamin D mediated by vitamin D receptors (VDR)

Extra-renal tissues that can convert circulating 25(OH)D to the biologically active 1,25(OH)$_2$D$_3$:

- Mammary
- Colon
- Prostate
- Skin
- Ovary
- Brain
- Pancreas (β-islet cells)
- Vascular smooth muscles

*25OHD 1α-hydroxylase (CYP27B1) requires an adequate amount of substrate [25(OH)D] for regulation.*
Causes and Consequences

Vitamin D Deficiency

Causes
- Sunscreen
- Melanin
- Latitude
- Winter
- Medications and Supplements
  - Antiseizure medications
  - Glucocorticoids
  - Rifampin
  - HAART
  - St John’s wort
- Hepatic failure
- Renal failure
- Nephrotic syndrome
- Obesity
- Malabsorption
  - Crohn’s disease
  - Whipple
  - Cystic fibrosis
  - Celiac disease
  - Liver disease

Consequences
- Consequences
  - Alzheimer
  - Schizophrenia
  - Depression
  - Neurocognitive dysfunction
- Infections
  - Upper respiratory tract
  - Tuberculosis
  - Influenza A
  - FEV1
  - Asthma
  - Wheezing diseases
  - High blood pressure
  - Congestive heart failure
  - Myocardial Infarction
  - Peripheral vascular disease
  - Hypertension
  - AODM
  - Metabolic syndrome
  - Pre-eclampsia
  - Cesarean section
  - Osteoporosis
  - Muscle weakness
  - Muscle aches
  - Osteoarthritis
  - Osteomalacia
  - Rickets
- Cancer
  - Breast
  - Colon
  - Prostate
  - Pancreas
- Autoimmune diseases
  - Type 1 diabetes mellitus
  - Multiple sclerosis
  - Crohn’s disease
  - Rheumatoid arthritis

Holick, M. F. Nat. Rev. Endocrinol. 7, 73-75 (2011); doi:10.1038/nrendo.2010.234
Defining Optimal Vitamin D Status

Based on a population model to prevent vitamin D deficiency in 97.5% of the general population with a focus on bone health.

Institute of Medicine (IOM)

Recommendation
≥ 50 nmol/L

Based on a medical model to prevent vitamin D deficiency and avoid other risks related to inadequate vitamin D status.

Endocrine Society Guidelines

Recommendation
≥ 75 nmol/L

Summary of Recommendations

1.0 Diagnostic Procedure

1.1 We recommend screening for vitamin D deficiency in individuals at risk for deficiency. We do not recommend population screening for vitamin D deficiency in individuals who are not at risk (I-3).

1.2 We recommend using the serum circulating 25-hydroxyvitamin D (25(OH)D) level, measured by a reliable assay, to establish vitamin D status in patients who are at risk for vitamin D deficiency. Vitamin D deficiency is defined as a 25(OH)D level below 20 ng/mL (50 nmol/L). We do not recommend using the serum 24-hour urinary cyclic adenosine monophosphate (cAMP) assay for this purpose and are in favor of using an assay that is readily accessible under normal circumstances, such as 25(OH)D deficiency in patients with osteoporosis, elderly patients, and patients with chronic illness. We also recommend that the 25(OH)D level be measured in the same month as the urinary cAMP assay.

End Note

1. Although it is not currently recommended for routine screening, the 25(OH)D level can be measured using a commercially available immunoassay. It is important to note that the cAMP assay is not currently recommended for routine screening of vitamin D status, as it is not widely available and lacks standardization.
Over 1 billion individuals worldwide are vitamin D deficient or insufficient.

Serum 25-hydroxyvitamin D concentration <30 nmol/L

Adapted from Holick et al. J Clin Endocrinol Metab 2012;97(4):1153-58
Presentation Overview

1. Vitamin D, Bone Density and Fracture Risk
2. Vitamin D, Muscle Function and Falls Risk
3. Non-skeletal Effects of Vitamin D
4. “D”-livering the Message: Interpreting the Data
Vitamin D is essential for ensuring intestinal absorption of calcium

- Without vitamin D only 10-15% of dietary calcium is absorbed; reports that maximal Ca absorption occurs at a 25OHD level ~80 nmol/L. Heaney et al. Am J Clin Nutr 2004
- Others report a linear increase in Ca absorption or no increase when baseline 25OHD exceeds 25-30 nmol/L. Aloia et al AJCN 2014; Gallagher et al JCEM 2012; Bouillon et al JCEM 2013

Regulation of parathyroid hormone (PTH) to maintain serum calcium

- Some reports that serum PTH levels plateau at a 25OHD level of 50-75 nmol/L. Chapuy et al. Osteop Int 1997
- Recent data suggested that there is no threshold as defined by suppression of PTH with 25OHD levels between 15–150 nmol/L Sai et al. J Clin Endocrinol Metab 2011
Defining Optimal Vitamin D Status

Histomorphometric Analysis of Iliac Crest Bone Biopsies from 675 individuals from Germany

Red line indicates the threshold of 2% osteoid volume used in this study as a conservative histopathologic border to osteomalacia. Yellow line indicates the threshold of 1.2% osteoid volume used by other studies.


Priefel al J Bone Miner Res 2010; 25:305-312.
A systematic review and meta-analysis of 23 RCTs

[4082 adults (92% women, average age of 59 years)]

No effect on spinal BMD

Increase in FN BMD (marked heterogeneity)

Reid et al. Lancet. 2014 Jan 11;383(9912):146-55
**Vitamin D Treatment and BMD**

**Subgroup Analysis: Systematic Review and Meta-analysis**

- **Baseline Serum 25(OH)D concentrations**
  Non-significant trend for greater benefits (BMD 0.6 – 1.0%) in those with baseline serum 25OHD <50 nmol/L; no additional benefit if ≥50 nmol/L.

- **Vitamin D dose**
  No effect of vitamin D at doses ≥800 IU/d; some benefits observed at lower doses (<800 IU/d)?

- **Duration of Treatment**
  Duration of vitamin D therapy (≤12 vs >12 months) did not appear to influence the responses.

- **Co-administration of Calcium**
  Co-administration of calcium did not affect the outcome.

Reid et al. Lancet. 2014 Jan 11;383(9912):146-55
Calcium + Vitamin D<sub>3</sub> Fortified Milk

Two year Randomised Controlled Trial: 167 men aged 50-87 yrs

- 2 x 200 ml tetra packs per day
- Ca 1000 mg/d + vit D<sub>3</sub> 800 IU/d
- UHT (Longlife) low fat (~1%)
- Compliance: 85.1% over 2 yrs

Results of 19 RCTs of Vitamin D ± Calcium on Fracture Risk

- **5 trials**: fracture risk was decreased.
- **10 trials**: no effect on fracture risk; in 3 of these trials falls incidence was decreased.
- **2 trials**: high dose supplementation was associated with an increased fracture risk.
Why Such Heterogeneous Findings?

Factors Contributing to the Marked Variability in the Findings

- **Adequate Dose of Vitamin D**
  Fracture prevention requires an adequate dose of vitamin D.

- **Baseline Serum 25OHD Values**
  Marked heterogeneity in the baseline values of serum 25(OH)D concentrations (and calcium).

- **Compliance with Treatment**
  Marked differences in compliance to the supplement regimens.

- **Genetic Factors**
  New genetic data might explain why there is considerable inter-individual variability in serum 25(OH)D in response to vitamin D therapy.
**Vitamin D Dose and Fracture Risk**

**Meta-analysis: Pooled Analysis of Vitamin D Dose Requirements**
(11 RCTs, adults ≥65 years, 31,022 persons, mean age 76 years; 91% women)

- **Hip Fracture**
  - Relative Risk (95% CI)
  - Ref
  - ITT analysis: a non-significant 10% ↓ risk
  - 30% ↓ risk

- **Any Non-vertebral Fx**
  - Relative Risk (95% CI)
  - Ref
  - ITT analysis: a significant 7% ↓ risk
  - 14% ↓ risk

**Per Protocol Analysis**: Actual intake = assigned intake + additional supplements (adj. for adherence to suppl.)

**Most of the trials with vitamin D doses > 800 IU/d also supplemented with calcium**

Bischoff-Ferrari et al. N Eng J Med 2012;367;1 July 5
Vitamin D Status and Fracture Risk

Serum Vitamin D Status: Dose-Response Relationship

**Hip Fracture (n=313)**

- Serum 25(OH)D ≥ 61 nmol/L, hip fracture risk ↓ 37%

**Any Non-vertebral Fx (n=914)**

- Serum 25(OH)D ≥ 61nmol/L, non-vertebral fx risk ↓ 31%

Most of the trials with vitamin D doses > 800 IU/d also supplemented with calcium

Bischoff-Ferrari et al. N Eng J Med 2012;367;1 July 5
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**Meta-analysis: Pooled Analysis of Vitamin D Dose Requirements**

No interactions between vitamin D, age, type of dwelling, baseline 25(OH)D or calcium

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group</th>
<th>Control Group</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
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<tbody>
<tr>
<td><strong>Hip Fracture</strong></td>
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<tr>
<td><strong>Age</strong></td>
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<td></td>
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<tr>
<td>All</td>
<td>151</td>
<td>586</td>
<td>0.70 (0.58–0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>13</td>
<td>128</td>
<td>0.72 (0.59–1.31)</td>
<td>0.27</td>
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<tr>
<td>75–84 yr</td>
<td>130</td>
<td>337</td>
<td>0.77 (0.58–0.99)</td>
<td>0.003</td>
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<tr>
<td>≥85 yr</td>
<td>8</td>
<td>126</td>
<td>0.54 (0.25–1.20)</td>
<td>0.13</td>
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<td><strong>Type of dwelling</strong></td>
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<tr>
<td>All</td>
<td>151</td>
<td>586</td>
<td>0.70 (0.58–0.86)</td>
<td>&lt;0.001</td>
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<td>Community dwelling</td>
<td>42</td>
<td>253</td>
<td>0.68 (0.48–0.96)</td>
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<td>Institution</td>
<td>109</td>
<td>333</td>
<td>0.70 (0.55–0.89)</td>
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<td><strong>Baseline 25(OH)D</strong></td>
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<td>All†</td>
<td>11</td>
<td>177</td>
<td>0.55 (0.29–1.05)</td>
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<td>&lt;30 nmol/liter</td>
<td>2</td>
<td>42</td>
<td>0.40 (0.08–1.91)</td>
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<td>≥30 nmol/liter</td>
<td>9</td>
<td>135</td>
<td>0.60 (0.29–1.22)</td>
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<td><strong>Calcium Intake</strong></td>
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<tr>
<td>All</td>
<td>123</td>
<td>368</td>
<td>0.71 (0.56–0.88)</td>
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<tr>
<td>&lt;1000 mg</td>
<td>6</td>
<td>359</td>
<td>0.65 (0.25–1.68)</td>
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<tr>
<td>≥1000 mg</td>
<td>117</td>
<td>9</td>
<td>0.77 (0.30–1.96)</td>
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<table>
<thead>
<tr>
<th></th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td><strong>Any Nonvertebral Fx</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.86 (0.76–0.96)</td>
<td>0.007</td>
</tr>
<tr>
<td>65–74 yr</td>
<td>1.09 (0.90–1.33)</td>
<td>0.39</td>
</tr>
<tr>
<td>75–84 yr</td>
<td>0.76 (0.66–0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥85 yr</td>
<td>0.87 (0.59–1.30)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Bischoff-Ferrari et al. N Eng J Med 2012;367;1 July 5
Vitamin D + Calcium and Fracture Risk

Community-dwelling vs. Institutionalized Elderly

Meta-analysis on the effects of vitamin D and calcium on hip fractures

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium/ Vitamin D n/N</th>
<th>Control n/N</th>
<th>Relative Risk/ Hazard Ratio [95% confidence interval]</th>
<th>Weight (%)</th>
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</thead>
<tbody>
<tr>
<td>Dawson-Hughes, 1997</td>
<td>0/187</td>
<td>1/202</td>
<td>0.36 [0.02, 8.78] 0.6</td>
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<tr>
<td>Avenell CaD, 2004</td>
<td>1/35</td>
<td>1/35</td>
<td>1.00 [0.07, 15.4] 0.8</td>
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<tr>
<td>Harwood CaD, 2004</td>
<td>1/75</td>
<td>1/37</td>
<td>0.49 [0.03, 7.67] 0.8</td>
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<tr>
<td>Porthouse, 2005</td>
<td>8/1321</td>
<td>17/1993</td>
<td>0.71 [0.31, 1.64] 9</td>
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</tr>
<tr>
<td>RECORD CaD, 2005</td>
<td>46/1306</td>
<td>41/1332</td>
<td>1.14 [0.76, 1.73] 35</td>
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<tr>
<td>OSTPRE, 2010</td>
<td>4/1718</td>
<td>2/1714</td>
<td>2.00 [0.37, 10.9] 2</td>
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<tr>
<td>WHI 2013</td>
<td>70/4015</td>
<td>61/3957</td>
<td>1.20 [0.85, 1.69] 52</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Calcium/ Vitamin D n/N</th>
<th>Control n/N</th>
<th>Relative Risk/ Hazard Ratio [95% confidence interval]</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapuy 1994</td>
<td>137/1634</td>
<td>178/1636</td>
<td>0.77 [0.62, 0.95] 87</td>
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<tr>
<td>Chapuy 2002</td>
<td>27/389</td>
<td>21/194</td>
<td>0.64 [0.37, 1.10] 13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>164/2023</td>
<td>199/1830</td>
<td>0.75 [0.62, 0.92] P=0.005</td>
<td></td>
</tr>
</tbody>
</table>

Reid and Bolland Osteoporosis Int 2014 2014 Oct;25(10):2347-57

No effect

Risk ↓ 25%
Why Such Heterogeneous Findings?

Factors Contributing to the Marked Variability in the Findings

- **Adequate Dose of Vitamin D**
  Fracture prevention requires an adequate dose of vitamin D.

- **Baseline Serum 25OHD Values**
  Marked heterogeneity in the baseline values of serum 25(OH)D concentrations (and calcium).

- **Compliance with Treatment**
  Marked differences in compliance to the supplement regimens.

- **Genetic Factors**
  New genetic data might explain why there is considerable inter-individual variability in serum 25(OH)D in response to vitamin D therapy.
Calcium supplementation alone or calcium + vitamin D was associated with a 10-13% reduction in any fracture.

Treatment was associated with a reduced rate of bone loss at the hip [0.54% (95%CI, 0.35-0.73)] and spine [1.19% (95% CI, 0.76-1.61%)].

Compliance to treatment was associated with a greater risk reduction in fractures: 24% risk reduction if >80% compliance.

Those who were older, institutionalized, had low baseline calcium intake (<700 mg/d) and low serum 25(OH)D levels (<25 nmol/L) gained the most benefits.

Treatment effect was best with calcium doses of 1200 mg/d or more or vitamin D doses of 800 IU/d or more.

Tang BM et al 2007 Lancet 370:657
Presentation Overview

1. Vitamin D, Bone Density and Fracture Risk
2. Vitamin D, Muscle Function and Falls Risk
3. Non-skeletal Effects of Vitamin D
4. “D”-livering the Message: Interpreting the Data
1. **Proximal muscle weakness** is a prominent feature of the clinical syndrome of vitamin D deficiency.
   *Gelorup et al. Calcify Tissue Int 2000*

2. Specific **receptors** for vitamin D (VDR) are expressed in human muscle tissue, and their number decline with age.
   *Bischoff-Ferrari et al. J Bone Miner Res 2004*

3. **VDR knockout** (-/-) mice have small and variable muscle fibres.
   *Endo et al. Endocrinol 2003*

4. VDR activation may promote **de novo protein synthesis** in muscle.
   *Sorensen et al. Clan Sic 1979*

5. Promote **calcium transport** into the muscle cell; important for muscle contraction.
   *De Boland et al. Endocrinol 1987;120:1858-64*
Vitamin D Supplementation and Falls

**Falls Prevention by Dose of Vitamin D**

- Vitamin D dose of 700-1000 IU/d
  - 19% reduced the risk of falling

* Re-analysis of data: 34% reduced risk at higher doses (700-1000 IU/d)

**Falls Prevention by Serum 25(OH)D Level**

- Achieved serum 25OHD level ≥60 nmol/L
  - 23% reduced risk falling

* Most studies included Vitamin D + Calcium

Bischoff-Ferrari et al. BMJ 2009;339:b3692
**Factors that May Contribute to the Reduction in Falls Risk**

- **Vitamin D and Muscle Strength**
  2014 meta-analysis (29 RCTs): **positive** effect of vitamin D on muscle strength, especially lower limb strength.
  - **Greatest benefits**: institutionalized elderly, those with 25OHD initially <30 nmol/L and a change in 25OHD ≥25 nmol/L.
  

- **Vitamin D and Muscle Function**
  Meta-analysis of 13 RCTs found that vitamin D had a **beneficial** effect on postural sway and lower limb mobility.
  

- **Vitamin D, Type II Muscle Fibres and Power**
  Vitamin D has been shown to increase the size and number of **type II (fast twitch) muscle fibers**.
  
  2014 meta-analysis of 5 trials found **no effect** of vitamin D on muscle power (or muscle mass).
  
Elderly women aged >70 years
500,000 IU of cholecalciferol once a year for 3 to 5 years

Cumulative Incidence of Falls

- HR, 1.16 (95% CI, 1.05-1.28)
- \( P = .003 \)
- 16% ↑ falls risk

Cumulative Incidence of Fractures

- HR, 1.26 (95% CI, 0.99-1.59)
- \( P = .06 \)
- 26% ↑ fracture risk

Falls and fracture risk was greatest within the first 3 months after treatment

Sun Exposure and Falls Prevention

Effect of Sunlight Exposure on Falls and Function
12 month Randomised Controlled Trial

1. Sun exposure (20-30 min/d)
   - Residential Care (n=602)
   - Mean age 86.4 years (71% female)
   - Low baseline 25(OH)D = 32.9 nmol/L
   - 988 fall events and 50 low trauma fractures
   - Compliance with sun exposure poor
     - 70% attended ≥10%
     - 44% attended ≥30%
     - 17% attended >50%
   - No effect of sun exposure on fall risk
     (IRR 1.06, 95% CI 0.76-1.48)

2. Sun exposure (20-30 min/d) + Calcium
   - Attended >130 sessions/yr (>50%), falls were reduced
     (IRR 0.59, 95% CI 0.36-0.98)

3. Neither

Sambrook et al. Osteoporosis Int 2011
Vitamin D supplementation at doses of at least 800 IU/d can reduce the risk of falls.

- Greatest benefits on muscle function & falls risk is likely to be in those with low baseline levels (<30 nmol/L).
- High dose supplementation is not recommended.

Serum 25(OH)D levels ≥60 nmol/L have been linked to decreased falls.

- The absolute level of 25(OH)D needed to prevent falls is not known, but some evidence suggests that a minimum serum 25(OH)D level of 60 nmol/L is required to reduce falls risk.
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3. Non-skeletal Effects of Vitamin D
4. “D”-livering the Message: Interpreting the Data
Non-Skeletal Effects of Vitamin D

How Strong is the Level of Evidence?
Proposed Disease Incidence Prevention by Serum 25(OH)D Status

<table>
<thead>
<tr>
<th>Serum 25(OH)D nmol/L</th>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>150</th>
<th>175</th>
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<tr>
<td>Rickets</td>
<td>100%</td>
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<td>Osteomalacia</td>
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<td>Cancers, all combined</td>
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<td>Breast cancer</td>
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<td>Fractures, all combined</td>
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<td>Multiple sclerosis</td>
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<tr>
<td>Heart attack (men)</td>
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<tr>
<td>Peripheral vascular disease</td>
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<tr>
<td>Preeclampsia</td>
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<tr>
<td>Cesarean section</td>
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</tbody>
</table>

Of the 137 different outcomes reportedly linked to serum 25(OH)D, only 10 have been tested in clinical trials

Theodoratou et al. BMJ. 2014 Apr 1;348:g2035.
Vitamin D and Type 2 Diabetes

Risk of Developing Type 2 Diabetes by Serum 25(OH)D

5-year Prospective Study in 5200 Australian Adults (199 incident cases)

Each 25 nmol/L increment in 25OHD was associated with a 22% to 29% risk reduction of diabetes [OR (95% CI), 0.76 (0.63-0.92)]

P for trend: Model 1: P<0.001; Model 2: P=0.02; Model 3: P=0.02

Model 1: adjusted for age, ethnicity, WC, family history of diabetes, smoking status, PA (plus season and latitude for serum 25OHD).
Model 2: model 1 + hypertension and triglycerides; Model 3: model 2 + energy-adjusted magnesium; Model 4: model 2 + FPG

Risk of Type 2 Diabetes by Serum 25(OH)D Status

Meta-analysis of prospective studies [76,200 participants (4,996 incident cases)] observed that the risk of T2DM decreased by 38% in the highest vs lowest 25OHD category.

4% reduced risk per 10 nmol/L increment in serum 25(OH)D
[RR = 0.96 (95% CI 0.94-0.97)]
Risk of Cardiovascular Disease by Serum 25(OH)D Status

Meta-analysis of prospective studies [65,94 participants (6,123 incident cases)] observed that the risk of CVD decreased by 52% in the highest vs lowest 25OHD category.

### TABLE 1. Potential mechanisms and evidence to support a benefit for vitamin D and calcium in type 2 DM

<table>
<thead>
<tr>
<th>Improvement in pancreatic β-cell function</th>
<th>Improvement in insulin action</th>
<th>Improvement in systemic inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of specific vitamin D receptors in pancreatic β-cells (94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression of 1α-hydroxylase enzyme in pancreatic β-cells (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired insulin secretory response in mice lacking functional vitamin D receptors (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence of the vitamin D response element in the human insulin gene promotor (95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transcriptional activation of the human insulin gene by 1,25-OHD (96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency impairs glucose-mediated insulin secretion from rat pancreatic β-cells in vitro (13, 97–99) and in vivo (100, 101)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplementation with vitamin D restores insulin secretion in animals (13, 97, 99, 100, 102)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes and adequate [Ca²⁺] pool</td>
<td></td>
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</tr>
<tr>
<td>Regulation of calcium flux and [Ca²⁺] in the pancreatic β-cell via regulation of calbindin, a cytosolic calcium-binding protein (103)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alterations in calcium flux can have adverse effects on insulin secretion, a calcium-dependent process (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium depletion alone normalized glucose tolerance and insulin secretion in vitamin D-depleted rats (104)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In people without diabetes, hypocalcemia is associated with impairment of insulin release (105, 106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In diabetes patients, an oral calcium load augments glucose-induced insulin secretion (107)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with resistance to 1,25-OHD were found to have abnormal insulin secretion only if they were hypocalcemic (108)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement in insulin action</th>
<th>Calcium effect on insulin action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverse association between 25-OHD levels and sarcopenia (109)</td>
<td></td>
</tr>
<tr>
<td>Presence of vitamin D receptor in skeletal muscle (110)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D stimulates the expression of insulin receptor and enhances insulin responsiveness for glucose transport <em>in vitro</em> (26)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D directly activates peroxisome proliferator activator receptor-δ (111), a transcription factor implicated in the regulation of fatty acid metabolism in skeletal muscle and adipose tissue (112)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium influx through cell membranes and adequate [Ca²⁺] pool</td>
<td></td>
</tr>
<tr>
<td>Calcium is essential for insulin-mediated intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue (27–29) with a very narrow range of [Ca²⁺], needed for optimal insulin-mediated functions (30)</td>
<td></td>
</tr>
<tr>
<td>Changes in [Ca²⁺], in primary insulin target tissues contributes to alterations in insulin action (30–37)</td>
<td></td>
</tr>
<tr>
<td>Impairment of insulin receptor phosphorylation, a calcium-dependent process (115) leading to impaired insulin signal transduction (29, 34) and decreased glucose transporter-4 activity (34, 38)</td>
<td></td>
</tr>
<tr>
<td>[Ca²⁺] modulate adipocyte metabolism, which may promote lipid accumulation via increased <em>de novo</em> lipogenesis and inability to insulin-mediated lipolysis leading to fat accumulation (114, 115)</td>
<td></td>
</tr>
<tr>
<td>Type 2 DM exhibit impaired cellular calcium homeostasis including defects in skeletal muscle, adipocytes, and liver (116)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Improvement in systemic inflammation</th>
<th>Effects of vitamin D on cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D interacts with vitamin D response elements in the promotor region of cytokine genes to interfere with nuclear transcription factors implicated in cytokine generation and action (117–119)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D can down-regulate activation of nuclear factor-κB (117, 119, 120), which is an important regulator of genes encoding proinflammatory cytokines implicated in insulin resistance (121)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D interferes with cytokine generation by up-regulating expression of calbindin (94, 122, 123), a cytosolic calcium-binding protein found in many tissues including pancreatic β-cells (94, 123). Calbindin has been shown to protect against cytokine-induced apoptosis that may occur after a rise in cytosolic free calcium [Ca²⁺] (124).</td>
<td></td>
</tr>
<tr>
<td>Changes in [Ca²⁺], may lead to cytokine-induced apoptosis (85)</td>
<td></td>
</tr>
</tbody>
</table>
Vitamin D and Type 2 Diabetes

2014 Systematic Review and Meta-analysis of 35 RCTs

Trials of patients with normal glucose tolerance, pre-diabetes and type 2 diabetes

Key Findings:

- **No effect** of vitamin D treatment (in any group of patients) on:
  - Insulin sensitivity (HOMA-IR)
  - Glycated hemoglobin (HbA1c)
  - Fasting blood glucose levels
  - Progression toward diabetes

Overall, this meta-analysis of 35 RCTs involving 43,407 patients found no evidence for the use of vitamin D to prevent diabetes.
Vitamin D plus Calcium Fortified Yogurt

12 week RCT: 90 diabetic participants aged 30-60 years

Study Design

- Plain yogurt
  150 mg Ca/250 ml
- Vitamin D- fortified yogurt
  500 IU vitamin D + 150 mg Ca/250 ml
- Vitamin D + calcium fortified yogurt
  500 IU vitamin D + 250 mg Ca/250 ml

2 serves per day

*N* Serum 25OHD increased from 44 to 75 nmol/L

Vitamin D and Cardiovascular Disease

Systemic Review and Meta-Analysis of RCTs

- No significant effect of vitamin D supplementation on lipids, glucose or blood pressure.
- Trial data available to date are unable to demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D treatment.
- The quality of the available evidence is low to moderate at best.

Higher latitudes with low UVB exposure have been linked with an increased risk of colon, pancreatic, ovarian, breast and other cancers. (Grant WB Cancer, 2002; Grant WB Anticancer Res, 2012)

Prospective and retrospective epidemiological studies indicate that low 25(OH)D levels are associated with an increased risk of incident colorectal cancer as well as prostate and breast cancer, along with higher mortality rates from these cancers. (Holick et al N Eng J Med 357:3 July 19, 2007)

Other observational studies and meta-analyses have reported inconsistent or weak associations between dietary vitamin D and 25(OH)D with cancer risk. (Yin et al. Prev Med 2013; for a review refer to Rosen C J et al. Endocrine Reviews 2012;33:456-492)
Vitamin D and Cancer Incidence

Level II Evidence: Secondary Outcome from a RCT

Overall there was a 77% reduction in all cause cancer incidence

4-year double-blinded, placebo RCT
Post-menopausal women (n=1179)
Mean 25OHD at baseline: 72 nmol/L
Primary outcome: Fracture incidence
Secondary outcome: Cancer incidence
Randomised into either:
• Vit D₃ (1100 IU/d) + Ca (1450 mg/d)
• Calcium (1450 mg/d)
• Placebo

Limitation: Only 50 cancers cases during 4 years; 35 after the first year.
Vitamin D and Cancer Incidence

Secondary Analysis of Randomised Controlled Trials


- Men and women (n=2,686) aged 65-85 years, 5 year follow-up
- **100,000 IU vitamin D\(_3\)** tablets every 4 months
- Total cancer incidence: 14% vitamin D (n=188) 12.9% placebo (n=173)

Total cancer incidence: **HR = 1.09** (95% CI, 0.86, 1.36)

**Women’s Health Initiative (WHI Trial)**

- Women (n=36,282) aged 50-79 years; 7-year follow-up
- **Vitamin D 400 IU/d + Calcium 100 mg/d**

  - **Colorectal cancer** HR = **1.08** (95% CI, 0.86, 1.34)
  - **Breast cancer** HR = **0.96** (95% CI, 0.85, 1.09)


Re-analysis of the WHI trial including 15,646 women who were not taking personal calcium or vitamin D supplements at randomization revealed a significant decrease in the risk of total and breast cancer (14-20%) and a trend for a decrease in colorectal cancer (17%).

Vitamin D and Cancer Incidence

Analysis by Baseline Serum 25(OH)D Concentrations
Calcium and vitamin D supplement (WHI Trial) influence on breast cancer incidence

<table>
<thead>
<tr>
<th>Quintile</th>
<th>Baseline 25-hydroxyvitamin D (nmol/L)</th>
<th>Intervention OR (95% CI)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥67.6 nmol/L</td>
<td>81.9 ± 13.2</td>
<td>0.89 (0.58, 1.36)</td>
</tr>
<tr>
<td>55.4 to &lt;67.6 nmol/L</td>
<td>60.9 ± 3.5</td>
<td>1.25 (0.83, 1.90)</td>
</tr>
<tr>
<td>43.9 to &lt;55.4 nmol/L</td>
<td>49.2 ± 3.3</td>
<td>1.07 (0.70, 1.62)</td>
</tr>
<tr>
<td>32.4 to &lt;43.9 nmol/L</td>
<td>38.5 ± 3.3</td>
<td>0.69 (0.45, 1.06)</td>
</tr>
<tr>
<td>&lt;32.4 nmol/L</td>
<td>23.6 ± 5.9</td>
<td>0.91 (0.60, 1.39)</td>
</tr>
</tbody>
</table>

One would expect women with the lowest 25(OH)D concentrations at baseline to have the greatest magnitude of breast cancer reduction with randomization to the supplement group compared with the placebo group; this was NOT the case!

Vitamin D receptors (VDRs) are located within the brain, including the primary motor cortex and hippocampus.


VDRs and the enzymes responsible for the initial hydroxylation of vitamin D have been found within the majority of the CNS.


Vitamin D deficiency has been associated with a range of neurological diseases, including depression, cognitive decline, Alzheimer’s disease and Parkinson’s disease.

For review refer to Eyles et al Front Neuroendocrinol 2012; DeLuca et al. Neuro Appl Neurobiol 2013

The benefits of vitamin D on the nervous system include neurotransmission, neuroprotection and neuroplasticity.

Vitamin D and Cognitive Disorders

Prospective Cohort Studies

- Two recent prospective studies reported the serum 25OHD levels <50 nmol/L were related to cognitive impairment, and an increased risk of developing dementia or AD.

- A recent study proposed a threshold of serum 25OHD that is associated with cognitive disorders (<25 nmol/L).

Clinical Intervention Trials

- Few RCTs have examined the effects of vitamin D supplements on cognition.

- WHI Trial (7.8 year RCT, 4,034 women aged 65+ yrs) reported no effect of 400 IU/d Vit D + 1000 mg/d Ca on global cognitive function.
  Rossom et al JAGS 60:2197-2205, 2012

- A placebo RCT showed that 1,200 IU/d vitamin D$_3$ prevents deterioration in Parkinson’s disease patients over a 12-month period.
Vitamin D and Depression

Systemic Review and Meta-Analysis of RCTs

Adults at risk of depression, with depression symptoms or diagnosed with depression

Baseline serum 25OHD ranged from 47 to 100 nmol/L.
Vitamin D dose ranged from 1500 to 7100 IU/d.

Subgroup analysis: no effect of vitamin D dosage, baseline 25OHD level, sex, population (clinical or general) or sample (institutional or community) on depression.

Vitamin D and Depression

Comparing Studies With and Without Biological Flaws

Does rectifying vitamin D deficiency decrease depressive symptoms?

**Studies with Flaws**

- Dumville
- Sanders

### Meta-analysis

- Total (fixed effects)
- Total (random effects)

**Worsening of depression?**

-1.1 (95% CI -0.7, -1.5)

**Studies without Flaws**

- Jorde 0_12 mths DD_PP
- Jorde 0_12 mths DP_PP
- Khoraminya 0-2 wks
- Khoraminya 2_4 wks
- Khoraminya 4_6 wks
- Khoraminya 6_8 wks

### Meta-analysis

- Total (fixed effects)
- Total (random effects)

**Worsening of depression?**

0.78 (95% CI 0.24, 1.27)

- Similar baseline 25OHD (~55 nmol/L)
- Same dose of vitamin D (800 IU/d)
- Participants were both patients
- Used same outcome measure

Spedding S. Nutrients 214;6:1501-18
“Only one of the two studies reviewed showed a significant effect of vitamin D treatment on 25OHD levels in TB patients, and none of the clinical trials showed a significant effect of vitamin D on clinical outcome. Thus, evidence from RCTs does not support a reduction in TB infections with vitamin D treatment.

IOM, Dietary reference intakes for calcium and vitamin D, 2011

Patients lay in beds pushed out on the porches of the Texas Building of the Jewish Consumptives’ Relief Society for sun heliotherapy treatment for tuberculosis.
Vitamin D and Respiratory Tract Infections
Systematic Review and Meta-analysis of 11 RCTs of 5660 patients

Efficacy of Vitamin D for Prevention of RTI

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
</tr>
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<tbody>
<tr>
<td>Bias risk = High</td>
<td></td>
<td></td>
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<tr>
<td>Aloia</td>
<td>0.25</td>
<td>0.11</td>
<td>0.58</td>
</tr>
<tr>
<td>Jorde</td>
<td>0.93</td>
<td>0.62</td>
<td>1.64</td>
</tr>
<tr>
<td>Summary</td>
<td>0.50</td>
<td>0.14</td>
<td>1.80</td>
</tr>
<tr>
<td>Heterogeneity: $I^2$=84.1%, Q=6.3, df=1, p=0.0122</td>
<td></td>
<td></td>
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<tr>
<td>Bias risk = Low</td>
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<tr>
<td>Bergman</td>
<td>0.48</td>
<td>0.25</td>
<td>0.91</td>
</tr>
<tr>
<td>Camargo</td>
<td>0.49</td>
<td>0.31</td>
<td>0.79</td>
</tr>
<tr>
<td>Laaksi</td>
<td>0.67</td>
<td>0.38</td>
<td>1.17</td>
</tr>
<tr>
<td>Li-Ng</td>
<td>0.79</td>
<td>0.41</td>
<td>1.54</td>
</tr>
<tr>
<td>Majak</td>
<td>0.24</td>
<td>0.06</td>
<td>0.90</td>
</tr>
<tr>
<td>Manaseki-Holland 2010</td>
<td>0.60</td>
<td>0.41</td>
<td>0.88</td>
</tr>
<tr>
<td>Manaseki-Holland 2012</td>
<td>1.04</td>
<td>0.92</td>
<td>1.19</td>
</tr>
<tr>
<td>Murdoch</td>
<td>0.92</td>
<td>0.62</td>
<td>1.37</td>
</tr>
<tr>
<td>Urashima</td>
<td>0.53</td>
<td>0.28</td>
<td>0.99</td>
</tr>
<tr>
<td>Summary</td>
<td>0.67</td>
<td>0.50</td>
<td>0.88</td>
</tr>
<tr>
<td>Heterogeneity: $I^2$=79.5%, Q=27.2, df=8, p=0.0007</td>
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</tbody>
</table>

Summary: 0.64 [0.49; 0.84]  $I^2=72.4$, Q=38.7, df=10, p=0.001

Subgroup Analysis

- Primary endpoint (n=8) $p=0.35$
- Secondary endpoint (n=3) $p=0.24$
- Healthy subjects (n=8) $p=0.01$
- Patients (n=3) $p=0.8$
- Daily (n=7) $p=0.01$
- Bolus (n=3) $p=0.8$
- Children (n=5) $p=0.84$
- Adults (n=6) $p=0.8$
- Vit. D-sufficient (n=5) $p=0.8$
- Vit. D-insufficient (n=2) $p=0.8$

Vitamin D treatment associated with a 36% ↓ risk RTI

There was significant heterogeneity among studies

Vitamin D and Immune Function

Infant Vitamin D Supplementation and Incidence Type 1 Diabetes

- Finnish birth cohort study (10,821 children born in 1966)
- Main outcome was type 1 diabetes incidence in 1997 (81 cases).
- 88% of children were given vitamin D during first year.
- Vitamin D supplementation with 2000 IU/d reduced the risk of type 1 diabetes by approximately 78%.

*Adjusted for sex, neonatal (parity, gestational and maternal age), length of maternal education, social status, and standardised birth weight, and growth rate in infancy (suspected rickets adjusted in addition to the increased dose of vitamin D); †In children receiving vitamin D supplementation regularly.

Hypponen E et al. The Lancet 2001; 358(9292):1500-3
**Vitamin D and Multiple Sclerosis**

- **Living at higher latitudes** associated with an increased risk of MS
  - The risk of MS decreased by 41% for every 50 nmol/L increase in 25(OH)D above ~60 nmol/L

- Epidemiological and experimental evidence suggest that **poor vitamin D status** is related to an increased risk of developing MS.

- Higher serum 25(OH)D levels have been associated with decreased risk and exacerbation in **relapsing-remitting MS**.

At present the data from clinical trials is restricted, and does not allow any conclusion on the effect of high-dose vitamin D supplementation on disease course.
Presentation Overview

1. Vitamin D, Bone Density and Fracture Risk
2. Vitamin D, Muscle Function and Falls Risk
3. Non-skeletal Effects of Vitamin D
4. “D”-ivering the Message: Interpreting the Data
Vitamin D Status and Ill Health

Is Low Serum 25OHD Simply a Marker of Ill Health?

Prospective Cohort Studies (n=290)
- Moderate to strong **inverse associations** between 25(OH)D levels and CVD, lipids, inflammation, glucose metabolism, weight gain, infectious diseases, multiple sclerosis, mood disorders, cognitive function, muscle function and all-cause mortality.
- No association with cancer, except colorectal cancer.

Randomised controlled trials (n=172)
- **No effect** of vitamin D supplementation on disease occurrence, including colorectal cancer.
- Vitamin D seemed to **reduce** all-cause mortality.
- In 34 RCTs with a mean 25(OH)D levels <50 nmol/L at baseline, supplementation with ≥50 μg (2000 IU) per day **did not** show better results.

Autier et al. Lancet Diabetes Endocrinol 2014 2(1):76-89
Vitamin D deficiency is linked to chronic disease via reverse-causality or confounding:

- **Reverse causality (eg):**
  Vitamin D deficiency doesn’t cause dementia; dementia causes vitamin D deficiency because it causes people to stay indoors.

- **Confounding factor (eg):**
  Vitamin D deficiency does not cause dementia; a lack of UV exposure causes dementia and a lack of UV exposure causes D deficiency.

... the RCTs with null findings on vitamin D in non-skeletal disease are due to ‘methodological limitations and inadequate doses of vitamin D and inappropriate baseline levels of 25OHD that led to inept conclusions about vitamin D deficiency’

Professor Michael Holick


Autier et al. Lancet Diabetes Endocrinol 2014 2(1):76-89
• **Mixed findings** from epidemiological and observational studies.
  
  - *May depend on vitamin D status [25(OH)D] and the health status of the individual.*


• **Vitamin D supplementation** has had a **positive effect** on cytokine profiles in clinical patients, especially at higher doses (eg. up to 2000 IU/d).
  
  - *Congestive heart failure, multiple sclerosis, hemodialysis patients, T2DM & critically ill*

### Concept of ‘Biological Flaws’

## Are Different Levels Required for Non-Skeletal Diseases?

Included if baseline vitamin D status and supplemented dose was likely to have improved serum 25OHD levels.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Level of Evidence</th>
<th>Minimum Effective Serum 25OHD (nmol/L)</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature mortality</td>
<td>Level I</td>
<td>75</td>
<td>High level</td>
</tr>
<tr>
<td>Falls prevention</td>
<td>Level I</td>
<td>95</td>
<td>Moderate level</td>
</tr>
<tr>
<td>Cancer prevention</td>
<td>Level II</td>
<td>100</td>
<td>Low level</td>
</tr>
<tr>
<td>Respiratory infection prevention</td>
<td>Level II</td>
<td>95</td>
<td>Low level</td>
</tr>
<tr>
<td>Diabetes prevention</td>
<td>Level II</td>
<td>80</td>
<td>Low level</td>
</tr>
<tr>
<td>Depression treatment</td>
<td>Level II</td>
<td>75</td>
<td>Low level</td>
</tr>
<tr>
<td>Musculoskeletal pain management</td>
<td>Level II</td>
<td></td>
<td>Low level</td>
</tr>
<tr>
<td>Dental disease</td>
<td>Level III-2</td>
<td>&gt;84</td>
<td>Low level</td>
</tr>
<tr>
<td>Musculoskeletal strength</td>
<td>Level III-1</td>
<td></td>
<td>Low level</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>Level III-2</td>
<td>80</td>
<td>Low level</td>
</tr>
<tr>
<td>Health service utilisation</td>
<td>Level III-2</td>
<td></td>
<td>Low level</td>
</tr>
</tbody>
</table>

* Excluded trials with significant design flaws.

**Level I** Systematic review of Level II studies  
**Level II** Randomised controlled trial  
**Level III-1** Pseudo-randomised controlled trial  
**Level III-2** Comparative study with concurrent controls: non-randomised, experimental trial, cohort study, case-control study, or interrupted time series with a control group.

“D”-livering the Message

- Vitamin D deficiency is not rare; it affects over 1 billion people globally and people from all races, from young to old.

- **Level I evidence** from RCTs that vitamin D (plus calcium) can reduce the risk of falls and fractures and all-cause mortality.

- **Level II and III evidence** from ecological, case-control, retro- and prospective observational studies and interventions suggests that vitamin D plays a central role in a range of physiological functions and health outcomes.

There remains a need for large scale randomized controlled trials and dose-response data to evaluate the effects of vitamin D on chronic disease outcomes.