

# The Whitehall-Robins Report

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## The wide-ranging effects of vitamin D on health and disease

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Volume 10, Number 1 of The Whitehall-Robins Report from February 2001 reviewed general aspects of vitamin D nutrition and argued for higher official recommendations for adults<sup>1</sup>. This review updates the rapidly evolving picture of the potential health effects associated with our endemic lack of the sunshine vitamin.

One way to estimate the optimal intake for any nutrient is to focus on what would have been prevalent during the evolution of our species<sup>2</sup>. Those were the conditions for which our genome was designed, through natural selection. In this spirit, the accompanying figure offers a perspective of vitamin D nutritional status through human evolution. Our modern "normal" 25(OH)D concentrations are very low compared to the biological norms for our species<sup>3</sup>. We should ask whether this vitamin D-deprived, modern lifestyle may be affecting health beyond just bone.

### Summary of Vitamin D Metabolism

Vitamin D is metabolized quickly to calcidiol [25(OH)D], whose concentration in serum or plasma is the accepted way to quantify vitamin D nutritional status<sup>4</sup>. 25(OH)D is a prehormone in the same sense that testosterone and T4 are, because like them, it is the circulating, immediate precursor of a signaling molecule<sup>5</sup>. The kidney functions as a calcium-regulating gland that produces and secretes the hormone, calcitriol [1,25(OH)2D], into the bloodstream to stimulate absorption of calcium from food. A wider range of other tissues possess the 1-hydroxylase enzyme to generate 1,25(OH)2D for their local use<sup>6</sup> and receptors to respond to it<sup>7</sup>. These mechanisms account for the wide spectrum of health effects of UVB light and vitamin D.

### HEALTH EFFECTS OF VITAMIN D IN ADULTS SUPPORTED BY HIGHEST LEVEL OF EVIDENCE Osteoporosis

The one officially recognized indication for use of vitamin D in adults is the treatment and prevention of osteomalacia, bone loss and fractures. A recent meta-analysis of the use of vitamin D, 1,25(OH)2D and its analogs found *no evidence that doses of vitamin D less than 800 IU/day are effective* in preventing osteoporotic fractures. The good news was clear-cut prevention of osteoporosis-related fractures for older adults taking 800 IU/day of vitamin D<sup>8</sup>. Furthermore, pharmacological preparations of 1,25(OH)2D and its analogs were no better than conventional, nutritional vitamin D3. Trivedi, Doll and Kah added great strength to the vitamin D story with their study, in which 2686 adults (mostly men, age 65-85y) were randomized to either a placebo or a 100,000 IU vitamin D3 pill, taken just once every 4 months (826 IU/day, no extra calcium). The vitamin D resulted in a 39% reduction of any first fracture and a 22% reduction in the classic, osteoporosis-type fractures (vertebral, hip, or wrist)<sup>9</sup>.

Prevention of fracture is the *sin qua non* of osteoporosis evidence. While it is well accepted that bone loss in women accelerates for a few years after menopause, optimal research designs that involve fracture prevention are difficult before age 65 years because actual fractures of osteoporosis are rare at this time. This is a frustrating irony, because we should be doing research to develop strategies to prevent bone loss before it has progressed to the stage that fracture risk is high. One large epidemiologic study following nurses in the US did show that early postmenopausal women consuming over 12.5 mcg (500 IU)/day of vitamin D3 in food or

vitamin supplements exhibited 37% fewer hip fractures than women consuming <3.5 mcg (140 IU)/day<sup>10</sup> – surprisingly the study demonstrated the anti-fracture effect of calcium intake. To support further the effect of vitamin D on bone health are data from the large, US health survey, NHANES III. In white women under age 50, BMD was steadily higher as 25(OH)D increased to well beyond the normal range<sup>11</sup>. For those older than 50, the relationship was upwards to 100 nmol/L 25(OH)D, but BMD declined beyond that. The authors attributed the decline to "confounding by indication"; i.e. study participants had been given extra vitamin D because their BMD was low<sup>11</sup>.

### Effects on balance and muscle function

Within the first year of vitamin D treatment for osteoporosis, when bone density cannot have increased by enough to affect its quality, occurrence of fractures is reduced by about one third<sup>12</sup>. Vitamin D improves muscle strength and balance. This reduces the occurrence of the falls that cause fractures<sup>11;13-15</sup>. In the elderly, serum 25(OH)D concentrations correlate positively with muscle strength<sup>16</sup>.

### NON-BONE EFFECTS OF VITAMIN D STILL AWAITING CLINICAL TRIAL-BASED EVIDENCE

Vitamin D nutrition can mediate the non-classic (i.e. non-bone) effects. Blood levels of 25(OH)D are a far better reflection of the biological response and health effects of nutrition than are levels of 1,25(OH)2D.

### Cancer Prevention

Epidemiologic studies show that higher serum 25(OH)D, and/or environmental ultraviolet exposure are associated with 20-40% lower rates of breast, ovarian, prostate, and colorectal cancers<sup>17-24</sup>. Less rigorous statistical analyses also show relationships where higher UVB radiation is associated with less non-Hodgkin's lymphoma, and cancer of the bladder, esophagus, kidney, lung, pancreas, rectum, stomach and corpus uteri<sup>25</sup>. Cell culture studies show that 25(OH)D – physiologic concentrations. – prevent cellular proliferation of prostate tissue to a degree equivalent to the use of 100 times physiologic concentrations of 1,25(OH)2D<sup>26;27</sup>. This implies that vitamin D nutrition could be more effective than administration of the hormone.

### Multiple Sclerosis – Risk Of Disease

Multiple sclerosis is more prevalent in populations that have lower levels of vitamin D nutrition or ultraviolet exposure<sup>22;28-30</sup>. In Australia, people with

a childhood history of high sun exposure (>4 hr/day) are one third as likely as those reporting <2 hr/day to end up with MS<sup>31</sup>. These are associational studies that are highly suggestive, but not conclusive that additional vitamin D will play a role.

### Multiple Sclerosis – Effects On Active Disease

It is easy to overlook the fact that the mechanism of vitamin D to affect risk of acquiring disease can be different from the relevant mechanism functioning once the disease is present. Neurological lesions detectable by NMR in MS patients tend to increase in number during the winter, and decline in summer. This pattern parallels seasonal changes in 25(OH)D<sup>32</sup>. Since patients with MS experience heat-related fatigue or intolerance to sunshine, they avoid being outdoors. At the very least, people with MS are more likely to require vitamin D supplementation<sup>33</sup>; at best, this nutrient may function to moderate the disease.

### Diabetes Type 1

Vitamin D nutrition during infancy and childhood appears to protect against development of type 1 diabetes mellitus<sup>34;35</sup>. Like multiple sclerosis and schizophrenia, diabetes Type 1 is more common for people born during late winter<sup>36</sup>.

### Diabetes Type 2

Low levels of 25(OH)D are now clearly associated with insulin resistance and poor glucose tolerance<sup>37</sup>. Some contend that a lack of vitamin D contributes to syndrome X, the combination of hypertension, diabetes and obesity occurring in the same people<sup>38</sup>.

### Neurological disease and schizophrenia

The rat pups born to mothers that were vitamin D deficient exhibit major differences in brain anatomy<sup>39</sup>. For humans, birth in the seasons when 25(OH)D concentrations are lowest is associated with higher risk of schizophrenia, bipolar disorder, autism, Alzheimer's disease and amyotrophic lateral sclerosis<sup>40;41</sup>. These observations are consistent with the view that vitamin D is essential for fetal brain development<sup>42</sup>. Life in relatively sun deprived urban environments is implicated as a risk factor for schizophrenia in later years.

### Chronic pain syndromes

Muscle tenderness and weakness are classic features of vitamin D-deficient infants, and now we know that the same thing occurs in adults. Several studies show that low 25(OH)D levels are

associated with back and muscle pain that is alleviated through vitamin D supplementation<sup>43</sup>.

### Fibromyalgia/Chronic Fatigue Syndrome

Fibromyalgia patients are far more likely than healthy adults to exhibit low 25(OH)D levels<sup>43</sup>. While there is no proof that vitamin D deficiency causes fibromyalgia, lack of vitamin D is part of the vicious cycle associated with the condition. Illness results in less outdoor activity and poor nutrient intake. These result in vitamin D deficiency that causes further weakness and pain.

### Osteoarthritis

Established osteoarthritis progresses more slowly (is less severe) in adults with higher vitamin D nutritional status, with serum 25(OH)D that exceeds 75 nmol/L<sup>44,45</sup>.

### Blood Pressure

The prevalence of hypertension increases with population distance, north or south, from the equator<sup>46</sup>, and in epidemiologic studies, higher 25(OH)D levels correlate with lower diastolic pressure<sup>47</sup>. Tanning in vitamin D-forming UVB light lowers blood pressure of patients with mild hypertension<sup>48</sup>. One randomized intervention study showed vitamin D at 800 IU/d lowers blood pressure in the elderly<sup>49</sup>. The black American population tends to have greater prevalence of hypertension and lower 25(OH)D levels than white Americans<sup>50</sup>.

### Immune Function

Vitamin D deficiency impairs immune function in laboratory animals<sup>51</sup> and in children there is a strong association between pneumonia and rickets<sup>52</sup>.

### Congestive heart failure and cardiovascular disease

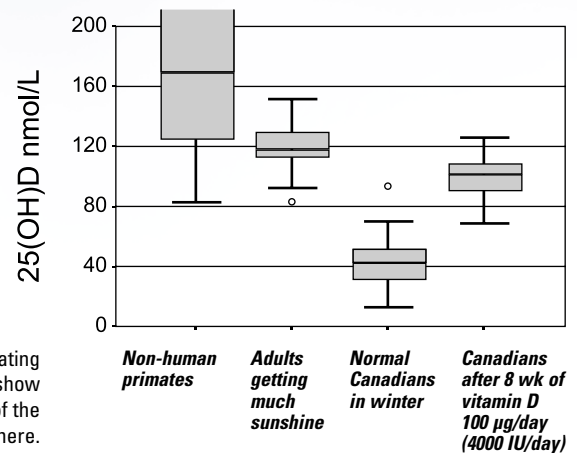
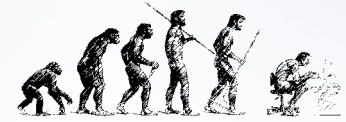
A natriuretic peptide associated with severity of cardiovascular disease correlates with 25(OH)D concentrations in patients with congestive heart failure<sup>53</sup>. The authors also showed that 25(OH)D was lower in patients with heart failure than in controls.

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### CONCLUSION

Years ago, nutrition books emphasized the risks of vitamin D. But considering what we are learning about this nutrient, the real danger is not in the consumption of too much, but that as a society, we are taking too little of it. All of the preceding evidence points to 25(OH)D concentrations higher than 70 nmol/L as the desirable target. On average, 10 mcg (400 IU)/day of vitamin D3 will raise an adult's 25(OH)D level by 10 nmol/L<sup>54</sup>.



Legend: Evolutionary perspective of circulating vitamin D nutritional status. Boxes show quartile values for 25(OH)D of the groups represented here.

The Whitehall-Robins Report is a Wyeth Consumer Healthcare Inc. publication that focuses on current issues on the role of vitamins and minerals in health promotion and disease prevention. Complimentary copies are distributed to Canadian health care professionals active or with a special interest in nutrition. Each issue is written and/or reviewed by independent health care professionals with expertise in the chosen topic.

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