Vitamin D

Sources and Physiological Functions

Vitamin D (calciferol) comprises a group of fat-soluble secosteroids found naturally in only a few foods. Some of those foods include fish-liver oils, fatty fish, mushrooms, egg yolks, and liver. The two major physiologically relevant forms of vitamin D are D_2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_3 is photosynthesized in the skin of vertebrates by solar ultraviolet (UV) B radiation on 7-dehydrocholesterol present in the skin (Fieser 1959). Vitamin D_2 is produced by the UV irradiation of ergosterol, which occurs in molds, yeast, and higher-order plants. Under conditions of regular sun exposure, the intake of dietary vitamin D is of minor importance. However, latitude, season, aging, sunscreen use, and skin pigmentation influence the skin's production of vitamin D_3 (Institute of Medicine 2011). In the United States, most of the dietary intake of vitamin D comes from fortified milk products and other fortified foods such as breakfast cereals and orange juice (Institute of Medicine 2011). Both vitamin D forms, vitamin D_2 and D_3, are available as prescriptions and over-the-counter supplements.

Vitamin D without a subscript represents either D_2, D_3, or both. Vitamin D is biologically inert. Whether derived from the skin or diet, vitamin D is short-lived in circulation (with a half-life of 1–2 days). It is either stored in fat cells or metabolized in the liver (Mawer 1972). In circulation, vitamin D is bound to vitamin D-binding protein and transported to the liver where it is converted to 25-hydroxyvitamin D [25(OH)D] (DeLuca 1984). This major circulating form of vitamin D is a good reflection of the cumulative effects of exposure to sunlight and dietary intake of vitamin D (Haddad 1973; Holick 1995). Therefore, it is used by clinicians to determine vitamin D status. To be biologically activated at physiologic concentrations, 25(OH)D must be converted in the kidneys to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. $1,25(OH)_2D$ is thought to be responsible for most—if not all—of the biological functions of vitamin D (DeLuca 1988; Reichel 1989). The production of 25(OH)D in the liver is a function of vitamin D availability from dietary intake and sun exposure, whereas production of $1,25(OH)_2D$ in the kidney is tightly regulated by mineral requirements. In the liver, vitamin D-25-hydroxylase is down-regulated by vitamin D and its metabolites, thereby limiting any increase in the circulating concentration of 25(OH)D following intakes or production of vitamin D after exposure to sunlight. In the kidney, in response to serum calcium and phosphorus concentrations, the production of $1,25(OH)_2D$ is regulated through the action of parathyroid hormone (PTH) (DeLuca 1988; Reichel 1989).

Health Effects

Active vitamin D (1,25-dihydroxyvitamin D) functions as a hormone, and its main biological function in people is to maintain serum calcium and phosphorus concentrations within the normal range. It does so by enhancing the efficiency of the small intestine to absorb these minerals from the diet (DeLuca 1988; Reichel 1989). When dietary calcium intake is inadequate to satisfy the body's calcium requirement, $1,25(OH)_2D$, along with PTH, mobilizes calcium stores from the bone. In the kidney, $1,25(OH)_2D$ increases calcium reabsorption by the distal renal tubules. Apart from these traditional calcium-related actions, $1,25(OH)_2D$ and its synthetic analogs are increasingly recognized for their potent anti-proliferative, pro-differentiative, and immunomodulatory activities (Nagpal 2005).

Vitamin D deficiency is characterized by inadequate mineralization or by demineralization of the skeleton. Among children, vitamin D deficiency is a common cause of bone deformities known as rickets. Vitamin D deficiency in adults leads to a mineralization defect in the skeleton, causing osteomalacia, and it induces secondary hyperparathyroidism with consequent bone loss and osteoporosis (Institute of Medicine 2011).

Researchers are investigating potential roles for vitamin D beyond bone health. Low serum vitamin D levels have been associated with a wide range of health conditions, including cardiovascular disease, mortality, diabetes, cancer, and autoimmune disorders. However, there is limited high-quality clinical evidence to guide screening and supplementation strategies (Kulie 2009). A report from the Agency for Healthcare Research and Quality (AHRQ) found that vitamin D supplementation has positive effects on bone health in postmenopausal women and older men (Cranney 2007). Another AHRQ report found that there was neither a significant association between vitamin D status and total cancer mortality, cancer risk, or cancer outcome, nor between vitamin D status and cardiometabolic outcomes including fasting glucose, blood pressure, myocardial infarction, or stroke (Chung 2009). Findings from large, randomized controlled trials showed no overall health benefits with vitamin D supplementation (Pittas 2010; Bouillon 2022). The VITAL, ViDA, and D2d trials, which together enrolled more than 30,000 participants, showed that vitamin D supplementation in adults with vitamin D-replete status (baseline serum 25(OH)D >50 nmol/L) does not reduce cancer risk, cardiovascular disease, falls, or progression to type 2 diabetes mellitus (Bouillon 2022). Complementing these trials, more than 60 Mendelian randomization studies—an approach that minimizes confounding bias—have examined the effects

of lifelong genetically lowered 25(OH)D levels on a range of health outcomes, with most reporting no significant effects (Bouillon 2022). Some studies suggested a potential increase in fall or fall-related events associated with higher vitamin D doses (Wanigatunga 2021; Waterhouse 2021). A draft recommendation from the U.S. Preventive Services Task Force advised against supplementation with vitamin D for primary prevention of falls and fractures in community-dwelling postmenopausal women and men aged 60 years and older (U.S. Preventive Services Task Force 2024). In 2024, the Endocrine Society produced a clinical practice guideline for vitamin D for the prevention of disease. The guideline recommends empiric vitamin D supplementation for ages 1 to 18 years, adults over 75 years of age, pregnant individuals, and high-risk prediabetic people through fortified foods and vitamin D supplementation (Demay 2024). For generally healthy adults, the guideline did not support routine vitamin D supplementation for broad prevention of major chronic disease and the panel advised against routine 25(OH)D testing without prior established indications.

Intake Recommendations

What constitutes the optimal intake of vitamin D remains a matter of disagreement. Recommendations from the Institute of Medicine (2011) specify an adequate intake (AI) of 400 international units (IU) [10 micrograms (µg)] of vitamin D per day for infants from birth through 12 months of age. The Dietary Guidelines for Americans recommend vitamin D supplementation for breastfed infants and infants who consume less than 32 ounces of infant formula per day (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2026). The dietary guidelines to meet the daily recommended intake are 400 IU (10 µg) for infants (0–12 months), 600 IU (15 µg) for persons 1 year and older, and 800 IU (20 µg) for those older than 70 years (Institute of Medicine 2011). Adequate intake of calcium and vitamin D is particularly important when peak bone mass is actively developing and accruing, for pregnant women, for vegetarians and vegans, and for older adults (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2026). In the United States, most dietary vitamin D is obtained from fortified foods, especially milk. In North America, the Tolerable Upper Intake Level for vitamin D is 4000 IU (100 µg) per day for individuals 9 years of age and older. The level ranges from 1000 IU to 3000 IU for infants and children less than 9 years of age. As intake increases above this amount, the potential risk for adverse consequences increases (Institute of Medicine 2011). Arguments have been put forward that daily doses of ≥4,000 IU of vitamin D convey some risks other than simple hypercalcemia or

hypercalciuria (Bouillon 2022). Such doses bring no benefits for vitamin D-replete adults but might cause loss of bone mineral density (Burt 2019) or increase the risk of falls (Smith 2017).

Biochemical Indicators and Cutoff Values

Currently, the concentration of serum 25(OH)D is the biomarker of choice to assess vitamin D status. Black persons have lower circulating 25(OH)D concentrations compared to White persons, yet have better bone health outcomes (Aloia 2008). It has been shown that serum 25(OH)D concentrations are lower in a state of inflammation (Haynes 2013; Antonelli 2023) and Black persons are known to have higher rates of low-grade inflammation (Wiley 2025). Therefore, inflammation may contribute to the lower measured vitamin D levels in Black compared to White persons. Other biomarkers, such as "free" 25(OH)D (Powe 2013; Aloia 2015; Alexandridou 2025), the portion of 25(OH)D that is not bound to vitamin D-binding protein, the ratio of 24,25-dihydroxyvitamin D to 25(OH)D (vitamin D metabolite ratio) (Berg 2015; Cashman 2015), and the active form 1,25-dihydroxyvitamin D (Bouillon 2013; Dirks 2018) are being explored to obtain additional clinical information (e.g., detect hypercalcemia, hereditary rickets, increased risk of fracture) (Dirks 2018; Ginsberg 2018).

The Institute of Medicine's Food and Nutrition Board suggested that persons with serum 25(OH)D concentrations of less than 30 nmol/L (12 ng/mL) are at risk for deficiency; those with concentrations of at least 30 but less than 50 nmol/L (12 to less than 20 ng/mL) are at risk for inadequacy; and those with concentrations between 50–75 nmol/L (20–30 ng/mL) are considered sufficient. The report indicated that concentrations greater than 125 nmol/L (50 ng/mL) may be reason for concern. Of interest to public health scientists, the report indicated that a serum 25(OH)D level consistent with the Estimated Average Requirement for dietary intake (EAR) lies between 30 and 50 nmol/L and that 40 nmol/L was selected from the middle of the range to serve as the targeted level for median dietary requirements (Institute of Medicine 2011).

Analytical Methods

To assess vitamin D status, one measures the concentration of 25(OH)D in serum, using either antibody-based methods such as radioisotope-, enzyme-linked- or chemiluminescence-based immunoassays, or using chemistry-based methods such as HPLC separation with UV or tandem mass spectrometry detection. HPLC-based methods separately measure 25(OH)D_2 and 25(OH)D_3 and these two metabolites are then summed up to constitute total 25(OH)D. Another metabolite that has recently received some attention is the C3-epimer of 25(OH)D_3. While the biological significance of this metabolite is not yet clear and serum concentrations are generally low compared to 25(OH)D_3 (Lutsey 2015; Cashman 2014), it is recommended to chromatographically separate this metabolite from 25(OH)D_3 to avoid misclassifying patients as having clinical vitamin D deficiency. Some clinical laboratories use conventional units for 25(OH)D (nanogram per milliliter [ng/mL]), whereas other laboratories use International System of Units (SI) (nanomole per liter [nmol/L]). The conversion factor to SI units is: 1 ng/mL = 2.5 nmol/L.

Method bias and imprecision problems have been reported with existing methods, particularly immuno-based assays (Carter 2007; Roth 2008; Wise 2025). A 2015 recommendation from the U.S. Preventive Services Task Force mentioned the inadequate quality of 25(OH)D testing methods as a limiting factor in confidently assessing the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults (LeFevre 2015). These problems highlighted a need to standardize clinical vitamin D measurements. To address this issue, reference methods were developed (Tai 2010; Stepman 2011; Mineva 2015) and used to assign accurate 25(OH)D target values for standard reference materials (Phinney 2012; Tai 2017). CDC introduced a Vitamin D Standardization Certification Program to help manufacturers improve the accuracy of their clinical vitamin D assay (https://www.cdc.gov/clinical-standardization-programs/index.html) using accuracy-based certified reference materials. Furthermore, the NIH has organized the Vitamin D

Standardization Program (VDSP) as a collaboration among U.S. government agencies (NIST, CDC), national survey laboratories, and vitamin D researchers worldwide (Sempos 2012).

A number of external quality assurance programs exist for serum or plasma 25(OH)D concentration measurements, including those sponsored by DEQAS (Vitamin D External Quality Assessment Scheme), the College of American Pathologists (Bone Markers and Vitamins Survey and Accuracy-Based Vitamin D Survey), and NEQAS (UK NEQAS EQA program for vitamin D). Standard reference materials (SRM 972a, 2970, 2973) with certified values for some or all vitamin D metabolites ($25(OH)D_2$, $25(OH)D_3$, and C3-epimer of $25(OH)D_3$) are available from the U.S. National Institute of Standards and Technology (NIST). An additional solvent-based reference material set (SRM 2972b) with certified values for $25(OH)D_2$ and $25(OH)D_3$ is also available.

Findings from NHANES

The National Health and Nutrition Examination Survey (NHANES) is the only source for nationally representative data on vitamin D for the U.S. population (Pfeiffer 2026a). Since 1988, NHANES has monitored the vitamin D status of the U.S. population. By design, this survey collects information and biological samples in the summer from people living at higher latitudes and in the winter from people living at lower latitudes. Because the different racial and ethnic groups are not evenly distributed across all geographic regions in the United States, the season-latitude structure of the survey can affect comparisons by race or ethnicity. In two seasonal subpopulations from NHANES III (1988–1994), Looker *et al.* (2002) found that in the winter 1–5% of the subpopulation residing at lower latitude had 25(OH)D concentrations below 25 nmol/L (10 ng/mL) and 25–57% below 62.5 nmol/L (25 ng/mL). In the summer, 1–3% and 21–49% of the subpopulation residing at higher latitude subpopulation had levels below these cutoffs, respectively. Mean 25(OH)D concentrations were highest in non-Hispanic White, intermediate in Mexican American, and lowest in non-Hispanic Black persons. An analysis of NHANES III and NHANES 2000–2004 (Looker 2008) showed that mean serum 25(OH)D levels were 5–9 nmol/L lower in 2000–2004 than in 1988–1994 in most males, but not in most females. Factors related to changes in vitamin D status were increased body mass index, decreased milk intake, and increased use of sun protection in the more recent surveys.

A radioimmunoassay (DiaSorin, Stillwater, MN) was used to measure serum 25(OH)D up to 2006. A 2009 expert roundtable on 25(OH)D in NHANES recommended the use of LC-MS/MS as a superior analytical technique going forward from 2007–2008 onward (Yetley 2010). To standardize the

original radioimmunoassay data to LC-MS/MS-equivalent data, representative specimens from NHANES between 1988 and 2006 were retested in a bridging study and regression equations were developed (Schleicher 2016a). The predicted LC-MS/MS-equivalent data, released on the NHANES website in October 2015, are the best data to use for correct interpretation of trends. Using the standardized serum 25(OH)D concentrations, no time trend was observed from 1988 to 2006, but during 2007–2010 concentrations were 5–6 nmol/L higher (Schleicher 2016b). The use of higher vitamin D supplement dosages coincided with this modest increase.

Data on 25(OH)D metabolites measured in NHANES 2007–2010 showed similar demographic patterns and strong correlations for total 25(OH)D, 25(OH)D_3 and the C3-epimer of 25(OH)D_3 (Schleicher 2016c). Concentrations of 25(OH)D_2 were detectable in 19% of the population, mainly in older persons, likely as a result of high-dose prescription vitamin D_2. The prevalence of persons at risk for vitamin D deficiency in the United States remained stable from 2003 to 2014, whereas the prevalence at risk for inadequacy declined slightly (Herrick 2019). Concentrations of 25(OH)D increased during the period of 2007 to 2014 in U.S. adults, however after adjusting for dietary supplement use the adjusted increase was no longer significant (Schleicher 2021). The percentage of persons taking higher dose vitamin D-containing supplements (≥1000 IU/day) increased steadily from 4% in 2007–2008 to 16% in 2013–2014 (Schleicher 2021).

An analysis of NHANES data from 2007–2008 to August 2021–August 2023 found a sharp increase in 25(OH)D concentrations >125 nmol/L ('may be of concern') from 2.0% to 11.4% and from 4.7% to 30.6% for those reporting 1 and ≥2 vitamin D supplements, respectively (Couch 2026). After adjusting for demographic changes over time, mean concentrations of 25(OH)D increased ~20% from NHANES 2001–2002 to August 2021–August 2023 (Pfeiffer 2026b). The prevalence of vitamin D insufficiency (25(OH)D <50 nmol/L) decreased over the same time period from ~28% to 22%, while the prevalence of excess vitamin D (25(OH)D >125 nmol/L) increased from <1% to 8%, with the highest prevalence in adult subgroups (16.2% in supplement users, 13.2% in females, and 12.3% in non-Hispanic White persons) (Pfeiffer 2026c).

A multiple regression analysis of NHANES 2003–2006 serum 25(OH)D concentrations showed that sociodemographic (age, education, income, race-ethnicity, and sex) and lifestyle (alcohol consumption, body mass index, dietary supplement use, physical activity, and smoking) variables together explained 23% of the biomarker variability (Schleicher 2013). Race-ethnic differences in serum 25(OH)D concentrations observed in crude univariate analysis remained significant after

adjusting for sociodemographic and lifestyle variables and use of dietary supplements (positive association) and BMI (negative association) were important correlates of serum 25(OH)D (Schleicher 2013). A second multiple regression analysis of NHANES 2003–2006 showed that after controlling for demographic variables, smoking, supplement use, fasting, inflammation, and renal function, inflammation was associated with significantly lower vitamin D concentrations (-3.9%), while fasting and impaired renal function were not associated (Haynes 2013). Pregnancy (in women 20–49 years of age) was associated with significantly higher vitamin D concentrations (6.6%) (Haynes 2013). A third multiple regression analysis of NHANES 2003–2006 evaluated sociodemographic, lifestyle, and physiologic factors as potential confounders or effect modifiers of the relationship between biomarkers and intake. The investigation demonstrated that dietary supplement use explains more variance in serum 25(OH)D concentrations than 24-hour dietary intake from food only (Sternberg 2026).

For more information about vitamin D, see the Institute of Medicine Dietary Reference Intake reports (Institute of Medicine 2011) and fact sheets from the National Institutes of Health, Office of Dietary Supplements (https://ods.od.nih.gov/factsheets/list-VitaminsMinerals/). A narrative review for vitamin D as part of a broader panel of neglected micronutrients has been published (Brown 2025).

Data in the 2026 tables

Data presented are from univariate analysis that was not adjusted for demographic variables (e.g., age, sex, race and Hispanic origin) or other blood concentration determinants (e.g., dietary intake, supplement use, smoking, BMI). Data for serum 25(OH)D were available from different NHANES cycles and have been generated using different methods. To allow for comparisons over time, NHANES released LC-MS/MS-equivalent data for NHANES 2001–2002, 2003–2004, and 2005–2006. Table footnotes indicate whether original or adjusted method data are presented.

Vitamin D biomarker	NHANES survey period	Method
Serum 25(OH)D	2001–2006	DiaSorin radioimmunoassay adjusted to LC-MS/MS
Serum 25(OH)D (total)	2007–2010, 2011–2018	LC-MS/MS
Serum 25(OH)D_3	2007–2010, 2011–2018	LC-MS/MS
Serum 25(OH)D_2	2007–2010, 2011–2018	LC-MS/MS
Serum 25(OH)D_3-epimer	2007–2010, 2011–2018	LC-MS/MS

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