National Institutes of Health
Office of Dietary Supplements

Vitamin D

Fact Sheet for Health Professionals

For information on vitamin D and COVID-19, see Dietary Supplements in the Time of COVID-19.

Introduction

Vitamin D (also referred to as "calciferol") is a fat-soluble vitamin that is naturally present in a few foods, added to others, and available as a dietary supplement. It is also produced endogenously when ultraviolet (UV) rays from sunlight strike the skin and trigger vitamin D synthesis.

Vitamin D obtained from sun exposure, foods, and supplements is biologically inert and must undergo two hydroxylations in the body for activation. The first hydroxylation, which occurs in the liver, converts vitamin D to 25-hydroxyvitamin D [25(OH)D], also known as "calcidiol." The second hydroxylation occurs primarily in the kidney and forms the physiologically active 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as "calcitriol" [1].

Vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal bone mineralization and to prevent hypocalcemic tetany (involuntary contraction of muscles, leading to cramps and spasms). It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts [1-3]. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in the body, including reduction of inflammation as well as modulation of such processes as cell growth, neuromuscular and immune function, and glucose metabolism [1-3]. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many tissues have vitamin D receptors, and some convert 25(OH)D to 1,25(OH)2D.

In foods and dietary supplements, vitamin D has two main forms, D_2 (ergocalciferol) and D_3 (cholecalciferol), that differ chemically only in their side-chain structures. Both forms are well

absorbed in the small intestine. Absorption occurs by simple passive diffusion and by a mechanism that involves intestinal membrane carrier proteins [4]. The concurrent presence of fat in the gut enhances vitamin D absorption, but some vitamin D is absorbed even without dietary fat. Neither aging nor obesity alters vitamin D absorption from the gut [4].

Serum concentration of 25(OH)D is currently the main indicator of vitamin D status. It reflects vitamin D produced endogenously and that obtained from foods and supplements [1]. In serum, 25(OH)D has a fairly long circulating half-life of 15 days [1]. Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). One nmol/L is equal to 0.4 ng/mL, and 1 ng/mL is equal to 2.5 nmol/L.

Assessing vitamin D status by measuring serum 25(OH)D concentrations is complicated by the considerable variability of the available assays (the two most common ones involve antibodies or chromatography) used by laboratories that conduct the analyses [5,6]. As a result, a finding can be falsely low or falsely high, depending on the assay used and the laboratory. The international Vitamin D Standardization Program has developed procedures for standardizing the laboratory measurement of 25(OH)D to improve clinical and public health practice [5,7-10].

In contrast to 25(OH)D, circulating 1,25(OH)2D is generally not a good indicator of vitamin D status because it has a short half-life measured in hours, and serum levels are tightly regulated by parathyroid hormone, calcium, and phosphate [1]. Levels of 1,25(OH)2D do not typically decrease until vitamin D deficiency is severe [2].

Serum concentrations of 25(OH)D and health
Although 25(OH)D functions as a biomarker of exposure, the extent to which 25(OH)D levels also serve as a biomarker of effect on the body (i.e., relating to health status or outcomes) is not clear [1,3].

Researchers have not definitively identified serum concentrations of 25(OH)D associated with deficiency (e.g., rickets), adequacy for bone health, and overall health. After reviewing data on vitamin D needs, an expert committee of the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that people are at risk of vitamin D deficiency at serum 25(OH)D concentrations less than 30 nmol/L (12 ng/mL; see Table 1 for definitions of "deficiency" and "inadequacy") [1]. Some people are potentially at risk of inadequacy at 30 to 50 nmol/L (12–20 ng/mL). Levels of 50 nmol/L (20 ng/mL) or more are sufficient for most people. In contrast, the Endocrine Society stated that, for clinical practice, a serum 25(OH)D concentration of more than 75 nmol/L (30 ng/mL) is necessary to maximize the effect of vitamin D on calcium, bone, and muscle metabolism [11,12]. The FNB committee also noted that serum concentrations greater than 125 nmol/L (50 ng/mL) can be associated with

adverse effects [1] (Table 1).

Table 1: Serum 25-Hydroxyvitamin D [25(OH)D] Concentrations and Health [1]

nmol/L*	ng/mL*	Health status
<30	<12	Associated with vitamin D deficiency, which can lead to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Linked to potential adverse effects, particularly at >150 nmol/L (>60 ng/mL)

*Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). One nmol/L = 0.4 ng/mL, and 1 ng/mL = 2.5 nmol/L.

Optimal serum concentrations of 25(OH)D for bone and general health have not been established because they are likely to vary by stage of life, by race and ethnicity, and with each physiological measure used [1,13,14]. In addition, although 25(OH)D levels rise in response to increased vitamin D intake, the relationship is nonlinear [1]. The amount of increase varies, for example, by baseline serum levels and duration of supplementation.

Recommended Intakes

Intake recommendations for vitamin D and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by expert committees of NASEM [1]. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and sex, include:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

An FNB committee established RDAs for vitamin D to indicate daily intakes sufficient to maintain bone health and normal calcium metabolism in healthy people. RDAs for vitamin D are listed in both micrograms (mcg) and international units (IU); 1 mcg vitamin D is equal to 40 IU (Table 2). Even though sunlight is a major source of vitamin D for some people, the FNB based the vitamin D RDAs on the assumption that people receive minimal sun exposure [1]. For infants, the FNB committee developed AIs based on the amount of vitamin D that maintains serum 25(OH)D levels above 20 ng/mL (50 nmol/L) and supports bone development.

Table 2: Recommended Dietary Allowances (RDAs) for Vitamin D [1]

Age	Male	Female	Pregnancy	Lactation
0-12 months*	10 mcg (400 IU)	10 mcg (400 IU)		
1–13 years	15 mcg (600 IU)	15 mcg (600 IU)		
14–18 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
19–50 years	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)	15 mcg (600 IU)
51–70 years	15 mcg (600 IU)	15 mcg (600 IU)		
>70 years	20 mcg (800 IU)	20 mcg (800 IU)		

*Adequate Intake (AI)

Many other countries around the world and some professional societies have somewhat different guidelines for vitamin D intakes [15]. These differences are a result of an incomplete understanding of the biology and clinical implications of vitamin D, different purposes for the guidelines (e.g., for public health in a healthy population or for clinical practice), and/or the use in some guidelines of observational studies in addition to randomized clinical trials to establish recommendations [9,15]. The Endocrine Society states, for example, that to maintain serum 25(OH)D levels above 75 nmol/L (30 ng/mL), adults might need at least 37.5 to 50 mcg (1,500–2,000 IU)/day of supplemental vitamin D, and children and adolescents might need at least 25 mcg (1,000 IU)/day [11]. In contrast, the United Kingdom government recommends intakes of 10 mcg (400 IU)/day for its citizens aged 4 years and older [16].

Sources of Vitamin D

Food

Few foods naturally contain vitamin D. The flesh of fatty fish (such as trout, salmon, tuna, and mackerel) and fish liver oils are among the best sources [17,1]. An animal's diet affects the amount of vitamin D in its tissues. Beef liver, egg yolks, and cheese have small amounts of vitamin D, primarily in the form of vitamin D_3 and its metabolite 25(OH)D_3. Mushrooms provide variable amounts of vitamin D_2 [17]. Some mushrooms available on the market have been treated with UV light to increase their levels of vitamin D_2. In addition, the Food and Drug Administration (FDA) has approved UV-treated mushroom powder as a food additive for use as a source of vitamin D_2 in food products [18]. Very limited evidence suggests no substantial differences in the bioavailability of vitamin D from various foods [19].

Animal-based foods typically provide some vitamin D in the form of 25(OH)D in addition to vitamin D_3. The impact of this form on vitamin D status is an emerging area of research. Studies show that 25(OH)D appears to be approximately five times more potent than the parent vitamin for raising serum 25(OH)D concentrations [17,20,21]. One study found that when the 25(OH)D content of beef, pork, chicken, turkey, and eggs is taken into account, the total amount of vitamin D in the food is 2 to 18 times higher than the amount in the parent vitamin alone, depending on the food [20].

Fortified foods provide most of the vitamin D in American diets [1,22]. For example, almost all of the U.S. milk supply is voluntarily fortified with about 3 mcg/cup (120 IU), usually in the form of vitamin D_3 [23]. In Canada, milk must be fortified with 0.88–1.0 mcg/100 mL (35–40 IU), and the required amount for margarine is at least 13.25 mcg/100 g (530 IU). Other dairy products made from milk, such as cheese and ice cream, are not usually fortified in the United States or Canada. Plant milk alternatives (such as beverages made from soy, almond, or oats) are often fortified with similar amounts of vitamin D to those in fortified cow's milk (about 3 mcg [120 IU]/cup); the Nutrition Facts label lists the actual amount [24]. Ready-to-eat breakfast cereals often contain added vitamin D, as do some brands of orange juice, yogurt, margarine, and other food products.

The United States mandates the fortification of infant formula with 1–2.5 mcg/100 kcal (40–100 IU) vitamin D; 1–2 mcg/100 kcal (40–80 IU) is the required amount in Canada [1].

A variety of foods and their vitamin D levels per serving are listed in Table 3.

Table 3: Vitamin D Content of Selected Foods [25]

Food	Micrograms (mcg) per serving	International Units (IU) per serving	Percent DV*
Cod liver oil, 1 tablespoon	34.0	1,360	170
Trout (rainbow), farmed, cooked, 3 ounces	16.2	645	81

Salmon (sockeye), cooked, 3 ounces	14.2	570	71
Mushrooms, white, raw, sliced, exposed to UV light, ½ cup	9.2	366	46
Milk, 2% milkfat, vitamin D fortified, 1 cup	2.9	120	15
Soy, almond, and oat milks, vitamin D fortified, various brands, 1 cup	2.5-3.6	100-144	13-18
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 1 serving	2.0	80	10
Sardines (Atlantic), canned in oil, drained, 2 sardines	1.2	46	6
Egg, 1 large, scrambled**	1.1	44	6
Liver, beef, braised, 3 ounces	1.0	42	5
Tuna fish (light), canned in water, drained, 3 ounces	1.0	40	5
Cheese, cheddar, 1.5 ounce	0.4	17	2
Mushrooms, portabella, raw, diced, ½ cup	0.1	4	1
Chicken breast, roasted, 3 ounces	0.1	4	1
Beef, ground, 90% lean, broiled, 3 ounces	0	1.7	0
Broccoli, raw, chopped, ½ cup	0	0	0
Carrots, raw, chopped, ½ cup	0	0	0
Almonds, dry roasted, 1 ounce	0	0	0
Apple, large	0	0	0
Banana, large	0	0	0
Rice, brown, long-grain, cooked, 1 cup	0	0	0
Whole wheat bread, 1 slice	0	0	0
Lentils, boiled, ½ cup	0	0	0
Sunflower seeds, roasted, ½ cup	0	0	0
Edamame, shelled, cooked, ½ cup	0	0	0

* DV = Daily Value. The FDA developed DVs to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin D is 20 mcg (800 IU) for adults and children aged 4 years and older [26]. The labels must list vitamin D content in mcg per serving and have the option of also listing the amount in IUs in parentheses. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.
** Vitamin D is in the yolk.

The U.S. Department of Agriculture's (USDA's) FoodData Central (https://fdc.nal.usda.gov/) lists the nutrient content of many foods and provides a comprehensive list of foods containing vitamin D

arranged by nutrient content (https://ods.od.nih.gov/pubs/usdandb/VitaminD-Content.pdf) and by food name (https://ods.od.nih.gov/pubs/usdandb/VitaminD-Food.pdf). However, FoodData Central does not include the amounts of 25(OH)D in foods.

Sun exposure

Most people in the world meet at least some of their vitamin D needs through exposure to sunlight [1]. Type B UV (UVB) radiation with a wavelength of approximately 290–320 nanometers penetrates uncovered skin and converts cutaneous 7-dehydrocholesterol to previtamin D_3, which in turn becomes vitamin D_3. Season, time of day, length of day, cloud cover, smog, skin melanin content, and sunscreen are among the factors that affect UV radiation exposure and vitamin D synthesis. Older people and people with dark skin are less able to produce vitamin D from sunlight [1]. UVB radiation does not penetrate glass, so exposure to sunshine indoors through a window does not produce vitamin D [27].

The factors that affect UV radiation exposure, individual responsiveness, and uncertainties about the amount of sun exposure needed to maintain adequate vitamin D levels make it difficult to provide guidelines on how much sun exposure is required for sufficient vitamin D synthesis [15,28]. Some expert bodies and vitamin D researchers suggest, for example, that approximately 5–30 minutes of sun exposure, particularly between 10 a.m. and 4 p.m., either daily or at least twice a week to the face, arms, hands, and legs without sunscreen usually leads to sufficient vitamin D synthesis [13,15,28]. Moderate use of commercial tanning beds that emit 2% to 6% UVB radiation is also effective [13,29].

But despite the importance of the sun for vitamin D synthesis, limiting skin exposure to sunlight and UV radiation from tanning beds is prudent [28]. UV radiation is a carcinogen, and UV exposure is the most preventable cause of skin cancer. Federal agencies and national organizations advise taking photoprotective measures to reduce the risk of skin cancer, including using sunscreen with a sun protection factor (SPF) of 15 or higher, whenever people are exposed to the sun [28,30]. Sunscreens with an SPF of 8 or more appear to block vitamin D-producing UV rays. In practice, however, people usually do not apply sufficient amounts of sunscreen, cover all sun-exposed skin, or reapply sunscreen regularly. Their skin probably synthesizes some vitamin D, even with typically applied sunscreen amounts [1,28].

Dietary supplements

Dietary supplements can contain vitamins D_2 or D_3. Vitamin D_2 is manufactured using UV irradiation of ergosterol in yeast, and vitamin D_3 is produced with irradiation of 7-dehydrocholesterol from lanolin and the chemical conversion of cholesterol [13]. Both forms raise serum 25(OH)D levels, and they seem to have equivalent ability to cure rickets [4]. In addition, most steps in the metabolism and actions of vitamins D_2 and D_3 are identical. However, most

evidence indicates that vitamin D_3 increases serum 25(OH)D levels to a greater extent and maintains these higher levels longer than vitamin D_2, even though both forms are well absorbed in the gut [31-34].

Some studies have used dietary supplements containing the 25(OH)D_3 form of vitamin D. Per equivalent microgram dose, 25(OH)D_3 is three to five times as potent as vitamin D_3 [35,36]. However, no 25(OH)D_3 dietary supplements appear to be available to consumers on the U.S. market at this time [37].

Vitamin D Intakes and Status

Most people in the United States consume less than recommended amounts of vitamin D. An analysis of data from the 2015–2016 National Health and Nutrition Examination Survey (NHANES) found that average daily vitamin D intakes from foods and beverages were 5.1 mcg (204 IU) in men, 4.2 mcg (168 IU) in women, and 4.9 mcg (196 IU) in children aged 2–19 years [38]. In fact, 2013–2016 NHANES data showed that 92% of men, more than 97% of women, and 94% of people aged 1 year and older ingested less than the EAR of 10 mcg (400 IU) of vitamin D from food and beverages [39].

The analysis of 2015–2016 data also showed that 28% of all individuals aged 2 years and older in the United States took a dietary supplement containing vitamin D [38]. In addition, 26% of participants aged 2–5 years and 14% of those aged 6–11 years took supplements; rates increased with age from 10% of those aged 12–19 years to 49% of men and 59% of women aged 60 and older. Total vitamin D intakes were three times higher with supplement use than with diet alone; the mean intake from foods and beverages alone for individuals aged 2 and older was 4.8 mcg (192 IU) but increased to 19.9 mcg (796 IU) when dietary supplements were included.

Some people take very high doses of vitamin D supplements. In 2013–2014, an estimated 3.2% of the U.S. adult population took supplements containing 100 mcg (4,000 IU) or more vitamin D [40].

One might expect a large proportion of the U.S. population to have vitamin D inadequacy on the basis of vitamin D intakes from foods, beverages, and even dietary supplements. However, comparing vitamin D intakes to serum 25(OH)D levels is problematic. One reason is that sun exposure affects vitamin D status, so serum 25(OH)D levels are usually higher than would be predicted on the basis of vitamin D dietary intakes alone [1]. Another reason is that animal foods contain some 25(OH)D. This form of vitamin D is not included in intake surveys and is considerably more potent than vitamins D_2 or D_3 at raising serum 25(OH)D levels [41].

An analysis of NHANES 2011–2014 data on serum 25(OH)D levels found that most people in the

United States aged 1 year and older had sufficient vitamin D intakes according to the FNB thresholds [42]. However, 18% were at risk of inadequacy (levels of 30–49 nmol/L [12–19.6 ng/mL]), and 5% were at risk of deficiency (levels below 30 nmol/L [12 ng/mL]). Four percent had levels higher than 125 nmol/L (50 ng/mL). Proportions at risk of deficiency were lowest among children aged 1–5 years (0.5%), peaked at 7.6% in adults aged 20–39 years, and fell to 2.9% among adults aged 60 years and older; patterns were similar for risks of inadequacy. Rates of deficiency varied by race and ethnicity: 17.5% of non-Hispanic Blacks were at risk of vitamin D deficiency, as were 7.6% of non-Hispanic Asians, 5.9% of Hispanics, and 2.1% of non-Hispanic White people. Again, the pattern was similar for the risk of inadequacy. Vitamin D status in the United States remained stable in the decade between 2003–2004 and 2013–2014.

Vitamin D Deficiency

People can develop vitamin D deficiency when usual intakes are lower over time than recommended levels, exposure to sunlight is limited, the kidneys cannot convert 25(OH)D to its active form, or absorption of vitamin D from the digestive tract is inadequate. Diets low in vitamin D are more common in people who have milk allergy or lactose intolerance and those who consume an ovo-vegetarian or vegan diet [1].

In children, vitamin D deficiency is manifested as rickets, a disease characterized by a failure of bone tissue to become properly mineralized, resulting in soft bones and skeletal deformities [43]. In addition to bone deformities and pain, severe rickets can cause failure to thrive, developmental delay, hypocalcemic seizures, tetanic spasms, cardiomyopathy, and dental abnormalities [44,45].

Prolonged exclusive breastfeeding without vitamin D supplementation can cause rickets in infants, and, in the United States, rickets is most common among breastfed Black infants and children [46]. In one Minnesota county, the incidence rate of rickets in children younger than 3 years in the decade beginning in 2000 was 24.1 per 100,000 [47]. Rickets occurred mainly in Black children who were breastfed longer, were born with low birthweight, weighed less, and were shorter than other children. The incidence rate of rickets in the infants and children (younger than 7) seen by 2,325 pediatricians throughout Canada was 2.9 per 100,000 in 2002–2004, and almost all patients with rickets had been breastfed [48].

The fortification of milk (a good source of calcium) and other staples, such as breakfast cereals and margarine, with vitamin D beginning in the 1930s along with the use of cod liver oil made rickets rare in the United States [28,49]. However, the incidence of rickets is increasing globally, even in the United States and Europe, especially among immigrants from African, Middle-Eastern, and Asian countries [50]. Possible explanations for this increase include genetic differences in vitamin D metabolism, dietary preferences, and behaviors that lead to less sun exposure [44,45].

In adults and adolescents, vitamin D deficiency can lead to osteomalacia, in which existing bone is incompletely or defectively mineralized during the remodeling process, resulting in weak bones [45]. Signs and symptoms of osteomalacia are similar to those of rickets and include bone deformities and pain, hypocalcemic seizures, tetanic spasms, and dental abnormalities [44].

Screening for vitamin D status is becoming a more common part of the routine laboratory bloodwork ordered by primary-care physicians, irrespective of any indications for this practice [6,51-53]. No studies have examined whether such screening for vitamin D deficiency results in improved health outcomes [54]. The U.S. Preventive Services Task Force (USPSTF) found insufficient evidence to assess the benefits and harms of screening for vitamin D deficiency in asymptomatic adults [6]. It added that no national professional organization recommends population screening for vitamin D deficiency.

Groups at Risk of Vitamin D Inadequacy

Obtaining sufficient vitamin D from natural (nonfortified) food sources alone is difficult. For many people, consuming vitamin D-fortified foods and exposing themselves to some sunlight are essential for maintaining a healthy vitamin D status. However, some groups might need dietary supplements to meet their vitamin D requirements. The following groups are among those most likely to have inadequate vitamin D status.

Breastfed infants
Consumption of human milk alone does not ordinarily enable infants to meet vitamin D requirements, because it provides less than 0.6 to 2.0 mcg/L (25 to 78 IU/L) [1,55,56]. The vitamin D content of human milk is related to the mother's vitamin D status; studies suggest that the breastmilk of mothers who take daily supplements containing at least 50 mcg (2,000 IU) vitamin D_3 have higher levels of the nutrient [56,57].

Although UVB exposure can produce vitamin D in infants, the American Academy of Pediatrics (AAP) advises parents to keep infants younger than 6 months out of direct sunlight, dress them in protective clothing and hats, and apply sunscreen on small areas of exposed skin when sun exposure is unavoidable [58]. The AAP recommends 10 mcg (400 IU)/day vitamin D supplements for exclusively and partially breastfed infants starting shortly after birth and lasting until they are weaned and consume at least 1,000 mL/day vitamin D-fortified formula or whole milk [56]. The AAP also recommends 10 mcg (400 IU)/day supplemental vitamin D for all infants who are not breastfed and ingest less than 1,000 mL/day vitamin D-fortified formula or milk. An analysis of NHANES 2009–2016 data found that only 20.5% of breastfed infants and 31.1% of infants who were not breastfed ingested these recommended amounts of supplements [59].

Older adults

Older adults are at increased risk of developing vitamin D insufficiency, partly because the skin's ability to synthesize vitamin D declines with age [1,60]. In addition, older adults are likely to spend more time than younger people indoors, and they might have inadequate dietary intakes of the vitamin [1].

People with limited sun exposure
Homebound individuals; people who wear long robes, dresses, or head coverings for religious reasons; and people with occupations that limit sun exposure are among the groups that are unlikely to obtain adequate amounts of vitamin D from sunlight [61]. The use of sunscreen also limits vitamin D synthesis from sunlight. However, because the extent and frequency of sunscreen use are unknown, the role that sunscreen may play in reducing vitamin D synthesis is unclear [1].

People with dark skin
Greater amounts of the pigment melanin in the epidermal layer of the skin result in darker skin and reduce the skin's ability to produce vitamin D from sunlight [1]. Black Americans, for example, typically have lower serum 25(OH)D levels than White Americans. However, whether these lower levels in persons with dark skin have significant health consequences is not clear [14]. Those of African American ancestry, for example, have lower rates of bone fracture and osteoporosis than do Whites (see the section below on bone health and osteoporosis).

People with conditions that limit fat absorption
Because vitamin D is fat soluble, its absorption depends on the gut's ability to absorb dietary fat [4]. Fat malabsorption is associated with medical conditions that include some forms of liver disease, cystic fibrosis, celiac disease, Crohn's disease, and ulcerative colitis [1,62]. In addition to having an increased risk of vitamin D deficiency, people with these conditions might not eat certain foods, such as dairy products (many of which are fortified with vitamin D), or eat only small amounts of these foods. Individuals who have difficulty absorbing dietary fat might therefore require vitamin D supplementation [62].

People who are obese or have undergone gastric bypass surgery
Individuals with a body mass index (BMI) of 30 or more have lower serum 25(OH)D levels than nonobese individuals. Obesity does not affect the skin's capacity to synthesize vitamin D. However, greater amounts of subcutaneous fat sequester more of the vitamin [1]. Obese people might need greater intakes of vitamin D to achieve 25(OH)D levels similar to those of people with normal weight [1,63,64].

Obese individuals who have undergone gastric bypass surgery can also become vitamin D deficient. In this procedure, part of the upper small intestine, where vitamin D is absorbed, is

bypassed, and vitamin D that is mobilized into the bloodstream from fat stores might not raise 25(OH)D to adequate levels over time [65,66]. Various expert groups—including the American Association of Metabolic and Bariatric Surgery, The Obesity Society, and the British Obesity and Metabolic Surgery Society—have developed guidelines on vitamin D screening, monitoring, and replacement before and after bariatric surgery [65,67]

Vitamin D and Health

The FNB committee that established DRIs for vitamin D found that the evidence was inadequate or too contradictory to conclude that the vitamin had any effect on a long list of potential health outcomes (e.g., on resistance to chronic diseases or functional measures), except for measures related to bone health. Similarly, in a review of data from nearly 250 studies published between 2009 and 2013, the Agency for Healthcare Research and Quality concluded that no relationship could be firmly established between vitamin D and health outcomes other than bone health [68]. However, because research has been conducted on vitamin D and numerous health outcomes, this section focuses on seven diseases, conditions, and interventions in which vitamin D might be involved: bone health and osteoporosis, cancer, cardiovascular disease (CVD), depression, multiple sclerosis (MS), type 2 diabetes, and weight loss.

Most of the studies described in this section measured serum 25(OH)D levels using various methods that were not standardized by comparing them to the best methods. Use of unstandardized 25(OH)D measures can raise questions about the accuracy of the results and about the validity of conclusions drawn from studies that use such measures and, especially, from meta-analyses that pool data from many studies that use different unstandardized measures [5,9,69]. More information about assay standardization is available from the Vitamin D Standardization Program (https://ods.od.nih.gov/Research/vdsp.aspx) webpage.

Bone health and osteoporosis

Bone is constantly being remodeled. However, as people age—and particularly in women during menopause—bone breakdown rates overtake rates of bone building. Over time, bone density can decline, and osteoporosis can eventually develop [70].

More than 53 million adults in the United States have or are at risk of developing osteoporosis, which is characterized by low bone mass and structural deterioration of bone tissue that increases bone fragility and the risk of bone fractures [71]. About 2.3 million osteoporotic fractures occurred in the United States in 2015 [72]. Osteoporosis is, in part, a long-term effect of calcium and/or vitamin D insufficiency, in contrast to rickets and osteomalacia, which result from vitamin D deficiency. Osteoporosis is most often associated with inadequate calcium intakes, but insufficient vitamin D intakes contribute to osteoporosis by reducing calcium absorption [1].

Bone health also depends on support from the surrounding muscles to assist with balance and postural sway and thereby reduce the risk of falling. Vitamin D is also needed for the normal development and growth of muscle fibers. In addition, inadequate vitamin D levels can adversely affect muscle strength and lead to muscle weakness and pain (myopathy) [1].

Most trials of the effects of vitamin D supplements on bone health also included calcium supplements, so isolating the effects of each nutrient is difficult. In addition, studies provided different amounts of nutrients and used different dosing schedules.

Clinical trial evidence on older adults

Among postmenopausal women and older men, many clinical trials have shown that supplements of both vitamin D and calcium result in small increases in bone mineral density throughout the skeleton [1,73]. They also help reduce fracture rates in institutionalized older people. However, the evidence on the impact of vitamin D and calcium supplements on fractures in community-dwelling individuals is inconsistent.

The USPSTF evaluated 11 randomized clinical trials of vitamin D and/or calcium supplementation in a total of 51,419 healthy, community-dwelling adults aged 50 years and older who did not have osteoporosis, vitamin D deficiency, or prior fractures [74,75]. It concluded that the current evidence was insufficient to evaluate the benefits and harms of supplementation to prevent fractures. In addition, the USPSTF recommended against supplementation with 10 mcg (400 IU) or less of vitamin D and 1,000 mg or less of calcium to prevent fractures in this population, but it could not determine the balance of benefits and harms from higher doses.

The USPSTF also reviewed the seven published studies on the effects of vitamin D supplementation (two of them also included calcium supplementation) on the risk of falls in community-dwelling adults aged 65 years or older who did not have osteoporosis or vitamin D deficiency. It concluded "with moderate certainty" that vitamin D supplementation does not reduce the numbers of falls or injuries, such as fractures, resulting from falls [76,76]. Another recent systematic review also found that vitamin D and calcium supplements had no beneficial effects on fractures, falls, or bone mineral density [78,79]. In contrast, a meta-analysis of 6 trials in 49,282 older adults found that daily vitamin D (10 or 20 mcg [400 IU or 800 IU]/day) and calcium (800 or 1,200 mg/day) supplementation for a mean of 5.9 years reduced the risk of any fracture by 6% and of hip fracture by 16% [80].

One systematic review and meta-analysis of 11 randomized, controlled trials published through 2018 of vitamin D supplementation alone (10–20 mcg [400–800 IU]/day or more at least every week or as rarely as once a year) for 9 months to 5 years found that the supplements provided no protection from fractures in 34,243 older adults [80].

Vitamin D supplements for bone health in minority populations

Bone mineral density, bone mass, and fracture risk are correlated with serum 25(OH)D levels in White Americans and Mexican Americans, but not in Black Americans [14,81]. Factors such as adiposity, skin pigmentation, vitamin D binding protein polymorphisms, and genetics contribute to differences in 25(OH)D levels between Black and White Americans.

One clinical trial randomized 260 Black women aged 60 years and older (mean age 68.2 years) to receive 60 to 120 mcg (2,400 to 4,800 IU) per day vitamin D_3 supplementation to maintain serum 25(OH)D levels above 75 nmol/L (30 ng/mL) for 3 years [82]. The results showed no association between 25(OH)D levels or vitamin D dose and the risk of falling in the 184 participants who completed the study. In fact, Black Americans might have a greater risk than White Americans of falls and fractures with daily vitamin D intakes of 50 mcg (2,000 IU) or more [14]. Furthermore, the bone health of older Black American women does not appear to benefit from raising serum 25(OH)D levels beyond 50 nmol/L (20 ng/mL) [82].

Vitamin D supplements and muscle function

Studies examining the effects of supplemental vitamin D on muscle strength and on rate of decline in muscle function have had inconsistent results [54]. One recent clinical trial, for example, randomized 78 frail and near-frail adults aged 65 years and older to receive 20 mcg (800 IU) vitamin D_3, 10 mcg 25(OH)D, or placebo daily for 6 months. The groups showed no significant differences in measures of muscle strength or performance [83]. Another study randomized 100 community-dwelling men and women aged 60 years and older (most were White) with serum 25(OH)D levels of 50 nmol/L (20 ng/ml) or less to 800 IU vitamin D_3 or placebo for 1 year [84]. Participants in the treatment group whose serum 25(OH)D level was less than 70 nmol/L (28 ng/ml) after 4 months received an additional 800 IU/day vitamin D_3. Despite increasing serum 25(OH)D levels to an average of more than 80 nmol/L (32 ng/ml), vitamin D supplementation did not affect lower-extremity power, strength, or lean mass.

Conclusions about vitamin D supplements and bone health

All adults should consume recommended amounts of vitamin D and calcium from foods and supplements if needed. Older women and men should consult their healthcare providers about their needs for both nutrients as part of an overall plan to maintain bone health and to prevent or treat osteoporosis.

Cancer

Laboratory and animal studies suggest that vitamin D might inhibit carcinogenesis and slow tumor progression by, for example, promoting cell differentiation and inhibiting metastasis. Vitamin D might also have anti-inflammatory, immunomodulatory, proapoptotic, and antiangiogenic effects [1,85]. Observational studies and clinical trials provide mixed evidence on

whether vitamin D intakes or serum levels affect cancer incidence, progression, or mortality risk.

Total cancer incidence and mortality

Some observational studies show associations between low serum levels of 25(OH)D and increased risks of cancer incidence and death. In a meta-analysis of 16 prospective cohort studies in a total of 137,567 participants who had 8,345 diagnoses of cancer, 5,755 participants died from cancer [86]. A 50 nmol/L (20 ng/mL) increase in 25(OH)D levels was associated with an 11% reduction in total cancer incidence rates and, in women but not men, a 24% reduction in cancer mortality rates. A meta-analysis of prospective studies that evaluated the association between serum 25(OH)D levels and cancer incidence (8 studies) or cancer mortality (16 studies) found that cancer risk decreased by 7% and cancer mortality rates decreased by 2% with each 20 nmol/L (8 ng/mL) increase in serum 25(OH)D levels [87]. Importantly, not all observational studies found higher vitamin D status to be beneficial, and the studies varied considerably in study populations, baseline comorbidities, and measurement of vitamin D levels.

Clinical trial evidence provides some support for the observational findings. For example, three meta-analyses of clinical trial evidence found that vitamin D supplementation does not affect cancer incidence but does significantly reduce total cancer mortality rates by 12–13% [88-90]. In the most recent meta-analysis, 10 randomized clinical trials (including the Vitamin D and Omega-3 Trial [VITAL] trial described below) that included 6,537 cancer cases provided 10 to 50 mcg (400 to 2,000 IU) vitamin D_3 daily (six trials) or 500 mcg (20,000 IU)/week to 12,500 mcg (500,000 IU)/year boluses of vitamin D_3 (four trials) [89]. The study reports included 3–10 years of followup data. The vitamin D supplements were associated with serum 25(OH)D levels of 54 to 135 nmol/L (21.6 to 54 ng/mL). Vitamin D supplementation reduced cancer mortality rates by 13%, and most of the benefit occurred with daily supplementation.

The largest clinical trial, VITAL, to investigate the effects of vitamin D supplementation on the primary prevention of cancer in the general population gave 50 mcg (2,000 IU)/day vitamin D_3 supplements with or without 1,000 mg/day marine omega-3 fatty acids or a placebo for a median of 5.3 years [91]. The study included 25,871 men aged 50 years and older and women aged 55 years and older who had no history of cancer, and most had adequate serum 25(OH)D levels at baseline. Rates of breast, prostate, and colorectal cancer did not differ significantly between the vitamin D and placebo groups. However, normal-weight participants had greater reductions in cancer incidence and mortality rates than those who were overweight or obese.

A few studies have examined the effect of vitamin D supplementation on specific cancers. Below are brief descriptions of studies of vitamin D and its association with, or effect on, breast, colorectal, lung, pancreatic, and prostate cancers.

Breast cancer

Some observational studies support an inverse association between 25(OH)D levels and breast cancer risk and mortality, but others do not [92-95]. The Women's Health Initiative clinical trial randomized 36,282 postmenopausal women to receive 400 IU vitamin D_3 plus 1,000 mg calcium daily or a placebo for a mean of 7 years [96]. The vitamin D_3 and calcium supplements did not reduce breast cancer incidence, and 25(OH)D levels at the start of the study were not associated with breast cancer risk [97].

In a subsequent investigation for 4.9 years after the study's end, women who had taken the vitamin D and calcium supplements (many of whom continued to take them) had an 18% lower risk of in situ (noninvasive) breast cancer [98]. However, women with vitamin D intakes higher than 15 mcg (600 IU)/day at the start of the trial and who received the supplements experienced a 28% increased risk of invasive (but not in situ) breast cancer.

Colorectal cancer

A large case-control study included 5,706 individuals who developed colorectal cancer and whose 25(OH)D levels were assessed a median of 5.5 years from blood draw to cancer diagnosis and 7,105 matched controls [99]. The results showed an association between 25(OH)D levels lower than 30 nmol/L (12 ng/mL) and a 31% higher colorectal cancer risk. Levels of 75 to less than 87.5 nmol/L (30 to less than 35 ng/mL) and 87.5 to less than 100 nmol/L (35 to less than 40 ng/mL) were associated with a 19% and 27% lower risk, respectively. The association was substantially stronger in women.

In the Women's Health Initiative clinical trial (described above), vitamin D_3 and calcium supplements had no effect on rates of colorectal cancer. In a subsequent investigation for 4.9 years after the study's end, women who had taken the vitamin D and calcium supplements (many of whom continued to take them) still had the same colorectal cancer risk as those who received placebo [98].

Another study included 2,259 healthy individuals aged 45 to 75 years who had had one or more serrated polyps (precursor lesions to colorectal cancer) that had been removed [100]. These participants were randomized to take 25 mcg (1,000 IU) vitamin D_3, 1,200 mg calcium, both supplements, or a placebo daily for 3–5 years, followed by an additional 3–5 years of observation after participants stopped the treatment. Vitamin D alone did not significantly affect the development of new serrated polyps, but the combination of vitamin D with calcium *increased* the risk almost fourfold. The VITAL trial found no association between vitamin D supplementation and the risk of colorectal adenomas or serrated polyps [101].

Lung cancer

A study of cohorts that included 5,313 participants who developed lung cancer and 5,313 matched controls found no association between serum 25(OH)D levels and risk of subsequent lung cancer, even when the investigators analyzed the data by sex, age, race and ethnicity, and smoking status [102].

Pancreatic cancer

One study comparing 738 men who developed pancreatic cancer to 738 matched controls found no relationship between serum 25(OH)D levels and risk of pancreatic cancer [103]. Another study that compared 200 male smokers in Finland with pancreatic cancer to 400 matched controls found that participants in the highest quintile of 25(OH)D levels (more than 65.5 nmol/L [26.2 ng/mL]) had a threefold greater risk of developing pancreatic cancer over 16.7 years than those in the lowest quintile (less than 32 nmol/L [12.8 ng/mL]) [104]. An investigation that pooled data from 10 studies of cancer in 12,205 men and women found that concentrations of 25(OH)D greater than 75 nmol/L (30 ng/mL) but less than 100 nmol/L (40 ng/mL) did not reduce the risk of pancreatic cancer. However, the results did show an increased risk of pancreatic cancer with 25(OH)D levels of 100 nmol/L (40 ng/mL) or above [105].

Prostate cancer

Research to date provides mixed evidence on whether levels of 25(OH)D are associated with the development of prostate cancer. Several studies published in 2014 suggested that high levels of 25(OH)D might increase the risk of prostate cancer. For example, a meta-analysis of 21 studies that included 11,941 men with prostate cancer and 13,870 controls found a 17% higher risk of prostate cancer for participants with higher levels of 25(OH)D [106]. What constituted a "higher" level varied by study but was typically at least 75 nmol/L (30 ng/mL). In a cohort of 4,733 men, of which 1,731 had prostate cancer, those with 25(OH)D levels of 45–70 nmol/L (18–28 ng/mL) had a significantly lower risk of the disease than men with either lower or higher values [107]. This U-shaped association was most pronounced for men with the most aggressive forms of prostate cancer. A case-control analysis of 1,695 cases of prostate cancer and 1,682 controls found no associations between 25(OH)D levels and prostate cancer risk [108]. However, higher serum 25(OH)D levels (at a cut point of 75 nmol/L [30 ng/mL]) were linked to a modestly higher risk of slow-growth prostate cancer and a more substantial lower risk of aggressive disease.

Since 2014, however, several published studies and meta-analyses have found no relationship between 25(OH)D levels and prostate cancer risk [109,110]. For example, an analysis was conducted of 19 prospective studies that provided data on prediagnostic levels of 25(OH)D for 13,462 men who developed prostate cancer and 20,261 control participants [111]. Vitamin D deficiency or insufficiency did not increase the risk of prostate cancer, and higher 25(OH)D concentrations were not associated with a lower risk.

Several studies have examined whether levels of 25(OH)D in men with prostate cancer are associated with a lower risk of death from the disease or from any cause. One study included 1,119 men treated for prostate cancer whose plasma 25(OH)D levels were measured 4.9 to 8.6 years after their diagnosis. Among the 198 participants who died (41 deaths were due to prostate cancer), 25(OH)D levels were not associated with risk of death from prostate cancer or any cause [112]. However, a meta-analysis of 7 cohort studies that included 7,808 men with prostate cancer found higher 25(OH)D levels to be significantly associated with lower mortality rates from prostate cancer or any other cause [113]. A dose-response analysis found that each 20 nmol/L [8 ng/mL] increase in 25(OH)D was associated with a 9% lower risk of both all-cause and prostate cancer-specific mortality.

For men with prostate cancer, whether vitamin D supplementation lengthens cancer-related survival is not clear. A meta-analysis of 3 randomized controlled trials in 1,273 men with prostate cancer found no significant differences in total mortality rates between those receiving vitamin D supplementation (from 10 mcg [400 IU]/day for 28 days to 45 mcg [1,800 IU] given in three doses total at 2-week intervals) and those receiving a placebo [114].

Conclusions about vitamin D and cancer

The USPSTF stated that, due to insufficient evidence, it was unable to assess the balance of benefits and harms of supplemental vitamin D to prevent cancer [115]. Taken together, studies to date do not indicate that vitamin D with or without calcium supplementation reduces the incidence of cancer, but adequate or higher 25(OH)D levels might reduce cancer mortality rates. Further research is needed to determine whether vitamin D inadequacy increases cancer risk, whether greater exposure to the nutrient can prevent cancer, and whether some individuals could have an increased risk of cancer because of their vitamin D status over time.

Cardiovascular disease

Vitamin D helps regulate the renin-angiotensin-aldosterone system (and thereby blood pressure), vascular cell growth, and inflammatory and fibrotic pathways [116]. Vitamin D deficiency is associated with vascular dysfunction, arterial stiffening, left ventricular hypertrophy, and hyperlipidemia [117]. For these reasons, vitamin D has been linked to heart health and risk of CVD.

Observational studies support an association between higher serum 25(OH)D levels and a lower risk of CVD incidence and mortality. For example, a meta-analysis included 34 observational studies that followed 180,667 participants (mean age greater than 50 years) for 1.3 to more than 32 years. The results showed that baseline serum 25(OH)D levels were inversely associated with total number of CVD events (including myocardial infarction, ischemic heart disease, heart failure, and stroke) and mortality risk [118]. Overall, the risk of CVD events was 10% lower for each 25

nmol/L (10 ng/mL) increase in serum 25(OH)D.

Another large observational study that followed 247,574 adults from Denmark for 0–7 years found that levels of 25(OH)D that were low (about 12.5 nmol/L [5 ng/mL]) and high (about 125 nmol/L [50 ng/mL]) were associated with a greater risk of mortality from CVD, stroke, and acute myocardial infarction [119]. Other meta-analyses of prospective studies have found associations between lower vitamin D status measured by serum 25(OH)D levels or vitamin D intakes and an increased risk of ischemic stroke, ischemic heart disease, myocardial infarction, and early death [120,121].

In contrast to the observational studies, clinical trials have provided little support for the hypothesis that supplemental vitamin D reduces the risk of CVD or CVD mortality. For example, a 3-year trial in New Zealand randomized 5,110 adults (mean age 65.9 years) to a single dose of 5,000 mcg (200,000 IU) vitamin D_3 followed by 2,500 mcg (100,000 IU) each month or a placebo for a median of 3.3 years [122]. Vitamin D supplementation had no effect on the incidence rate of myocardial infarction, angina, heart failure, arrhythmia, arteriosclerosis, stroke, venous thrombosis, or death from CVD. Similarly, the VITAL clinical trial described above found that vitamin D supplements did not significantly decrease rates of heart attacks, strokes, coronary revascularization, or deaths from cardiovascular causes [91]. Moreover, the effects did not vary by baseline serum 25(OH)D levels or whether participants took the trial's omega-3 supplement in addition to vitamin D.

However, another clinical trial designed to investigate bone fracture risk found that 800 IU/day vitamin D_3 (with or without calcium) or a placebo in 5,292 adults aged 70 years and older for a median of 6.2 years offered protection from cardiac failure, but not myocardial infarction or stroke [123].

High serum cholesterol levels and hypertension are two of the main risk factors for CVD. The data on supplemental vitamin D and cholesterol levels are mixed, as shown in one meta-analysis of 41 clinical trials in a total of 3,434 participants (mean age 55 years). The results of this analysis showed that 0.5 mcg (20 IU) to 214 mcg (8,570 IU)/day vitamin D supplementation (mean of 2,795 IU) for 6 weeks to 3 years reduced serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels, but not high-density lipoprotein cholesterol levels [124].

Studies of the effects of vitamin D supplements on hypertension have also had mixed findings. In one meta-analysis of 46 clinical trials that included 4,541 participants, vitamin D supplements (typically 40 mcg [1,600 IU]/day or less) for a minimum of 4 weeks had no significant effects on systolic or diastolic blood pressure [125]. In contrast, another meta-analysis of 30 clinical trials in 4,744 participants (mean age 54.5 years) that administered 5 mcg (200 IU) to 300 mcg (12,000

IU)/day vitamin D_3 for a mean of 5.6 months showed that more than 20 mcg (800 IU)/day significantly reduced systolic and diastolic blood pressure in normal-weight participants who had hypertension [126]. However, more than 20 mcg (800 IU)/day vitamin D_3, when taken with calcium supplements, significantly increased blood pressure in overweight and obese participants. Another meta-analysis of genetic studies in 146,581 participants (primarily adults) found that a low vitamin D status increased blood pressure and hypertension risk in people with genetic variants associated with low endogenous production of 25(OH)D [127].

Overall, clinical trials show that vitamin D supplementation does not reduce CVD risk, even for people with low 25(OH)D status (below 20 nmol/L [12 ng/mL]) at baseline [91,122].

Depression
Vitamin D is involved in various brain processes, and vitamin D receptors are present on neurons and glia in areas of the brain thought to be involved in the pathophysiology of depression [128].

A systematic review and meta-analysis of 14 observational studies that included a total of 31,424 adults (mean age ranging from 27.5 to 77 years) found an association between deficient or low levels of 25(OH)D and depression [128].

Clinical trials, however, do not support these findings. For example, a meta-analysis of 9 trials with a total of 4,923 adult participants diagnosed with depression or depressive symptoms found no significant reduction in symptoms after supplementation with vitamin D [129]. The trials administered different amounts of vitamin D (ranging from 10 mcg [400 IU]/day to 1,000 mcg [40,000 IU]/week). They also had different study durations (5 days to 5 years), mean participant ages (range, 22 years to 75 years), and baseline 25(OH)D levels; furthermore, some but not all studies administered concurrent antidepressant medications.

Three trials conducted since that meta-analysis also found no effect of vitamin D supplementation on depressive symptoms. One trial included 206 adults (mean age 52 years) who were randomized to take a bolus dose of 2,500 mcg (100,000 IU) vitamin D_3 followed by 500 mcg (20,000 IU)/week or a placebo for 4 months [130]. Most participants had minimal or mild depression, had a low mean baseline 25(OH) level of 33.8 nmol/L (13.5 ng/mL), and were not taking antidepressants. The second trial included 155 adults aged 60–80 years who had clinically relevant depressive symptoms, no major depressive disorder, and serum 25(OH)D levels less than 50 to 70 nmol/L (20 to 28 ng/mL) depending on the season; in addition, they were not taking antidepressants [131,132]. Participants were randomized to take either 30 mcg (1,200 IU)/day vitamin D_3 or a placebo for 1 year. In the VITAL trial described above, 16,657 men and women 50 years of age and older with no history of depression and 1,696 with an increased risk of recurrent depression (that had not been medically treated for the past 2 years) were randomized to take 50

mcg (2,000 IU)/day vitamin D_3 (with or without fish oil) or a placebo for a median of 5.3 years [133]. The groups showed no significant differences in the incidence and recurrent rates of depression, clinically relevant depressive symptoms, or changes in mood scores.

Overall, clinical trials did not find that vitamin D supplements helped prevent or treat depressive symptoms or mild depression, especially in middle-aged to older adults who were not taking prescription antidepressants. No studies have evaluated whether vitamin D supplements may benefit individuals under medical care for clinical depression who have low or deficient 25(OH)D levels and are taking antidepressant medication.

Multiple sclerosis

MS is an autoimmune disease of the central nervous system that damages the myelin sheath surrounding and protecting nerve cells in the brain and spinal cord. This damage hinders or blocks messages between the brain and body, leading to clinical features, such as vision loss, motor weakness, spasticity, ataxia, tremor, sensory loss, and cognitive impairment [134,135]. Some people with MS eventually lose the ability to write, speak, or walk.

The geographical distribution of MS around the world is unequal. Few people near the equator develop the disease, whereas the prevalence is higher further north and south. This uneven distribution has led to speculation that lower vitamin D levels in people who have less sunlight exposure might predispose them to the disease [135].

Many epidemiological and genetic studies have shown an association between MS and low 25(OH)D levels before and after the disease begins [135]. Observational studies suggest that adequate vitamin D levels might reduce the risk of contracting MS and, once MS is present, decrease the risk of relapse and slow the disease's progression [136]. One study, for example, tested 25(OH)D levels in 1,092 women in Finland an average of 9 years before their MS diagnosis and compared their outcomes with those of 2,123 similar women who did not develop MS [137]. More than half the women who developed MS had deficient or insufficient vitamin D levels. Women with 25(OH)D levels of less than 30 nmol/L (12 ng/mL) had a 43% higher MS risk than women with levels of 50 nmol/L (20 ng/mL) or higher. Among the women with two or more serum 25(OH)D samples taken before diagnosis (which reduced random measurement variation), a 50 nmol/L increase in 25(OH)D was associated with a 41% reduced risk of MS, and 25(OH)D levels less than 30 nmol/L were associated with an MS risk that was twice as high as levels of 50 nmol/L or higher.

Two earlier prospective studies of similar design—one in the United States with 444 non-Hispanic White individuals [138] and the other with 576 individuals in northern Sweden [139]—found that levels of 25(OH)D greater than 99.1 nmol/L (39.6 ng/mL) and at least 75 nmol/L (30 ng/mL),

respectively, were associated with a 61–62% lower risk of MS.

No clinical trials have examined whether vitamin D supplementation can prevent the onset of MS, but several have investigated whether supplemental vitamin D can help manage the disease. A 2018 Cochrane review analyzed 12 such trials that had a total of 933 participants with MS; the reviewers judged all of these trials to be of low quality [135]. Overall, vitamin D supplementation, when compared with placebo administration, had no effect on relevant clinical outcomes, such as recurrent relapse or worsened disability.

Experts have reached no firm consensus on whether vitamin D can help prevent MS given the lack of clinical trial evidence [140]. In addition, studies have not consistently shown that vitamin D supplementation tempers the signs and symptoms of active MS or reduces rates of relapse.

Type 2 diabetes

Vitamin D plays a role in glucose metabolism. It stimulates insulin secretion via the vitamin D receptor on pancreatic beta cells and reduces peripheral insulin resistance through vitamin D receptors in the muscles and liver [141]. Vitamin D might be involved in the pathophysiology of type 2 diabetes through its effects on glucose metabolism and insulin signaling as well as its ability to reduce inflammation and improve pancreatic beta-cell function [142,143].

Observational studies have linked lower serum 25(OH)D levels to an increased risk of diabetes, but their results might have been confounded by the fact that many participants were overweight or obese and were therefore more predisposed to developing diabetes and having lower 25(OH)D levels [1]. A review of 71 observational studies in adults with and without type 2 diabetes from 16 countries found a significant inverse relationship between vitamin D status and blood sugar levels in participants who did and did not have diabetes [144].

In contrast to observational studies, clinical trials provide little support for the benefits of vitamin D supplementation for glucose homeostasis. One trial included 65 overweight or obese adult men and women (mean age 32 years) who were otherwise healthy, did not have diabetes, and had low serum vitamin D levels (at or below 50 nmol/L [20 ng/mL]) [145]. The investigators randomly assigned participants to receive either a bolus oral dose of 2,500 mcg (100,000 IU) vitamin D_3 followed by 100 mcg (4,000 IU)/day or a placebo for 16 weeks. In the 54 participants who completed the study, vitamin D supplementation did not improve insulin sensitivity or insulin secretion in comparison with placebo.

One systematic review and meta-analysis evaluated 35 clinical trials that included 43,407 adults with normal glucose tolerance, prediabetes, or type 2 diabetes who received a median of 83 mcg (3,332 IU)/day vitamin D supplements or placebo for a median of 16 weeks [146]. Vitamin D had no significant effects on glucose homeostasis, insulin secretion or resistance, or hemoglobin A1c

levels (a measure of average blood sugar levels over the previous 2–3 months), irrespective of the study population, vitamin D dose, or trial quality.

Several trials have investigated whether vitamin D supplementation can prevent the transition from prediabetes to diabetes in patients with adequate 25(OH)D levels, and all have had negative results. In a trial in Norway, 511 men and women aged 25–80 years (mean age 62 years) with prediabetes received 500 mcg (20,000 IU) vitamin D_3 or a placebo each week for 5 years [147]. The results showed no significant differences in rates of progression to type 2 diabetes; in serum glucose, insulin, or hemoglobin A1c levels; or in measures of insulin resistance. At baseline, participants had an adequate mean serum 25(OH)D level of 60 nmol/L (24 ng/mL).

The largest trial to date of vitamin D supplements for diabetes prevention randomized 2,423 men and women aged 25 years and older (mean age 60 years) with prediabetes who were overweight or obese (mean BMI of 32.1) to 100 mcg (4,000 IU)/day vitamin D_3 or placebo for a median of 2.5 years [143]. Most participants (78%) had adequate serum levels of vitamin D at baseline (at least 50 nmol/L [20 ng/mL]). Vitamin D did not significantly prevent the development of diabetes in comparison with placebo. However, a post hoc analysis showed a 62% lower incidence of diabetes among participants with low baseline serum 25(OH)D levels (less than 30 nmol/L [12 ng/mL]) who took the vitamin D supplement than among those who took the placebo [143,148].

Studies have also assessed the value of vitamin D supplementation for managing diabetes, and they have found that the vitamin offers limited benefits. One meta-analysis of 20 clinical trials compared the effects of 0.5 mcg (20 IU)/day to 1,250 mcg (50,000 IU)/week vitamin D supplementation for 2–6 months with those of placebo on glycemic control in 2,703 adults from around the world who had diabetes [141]. The vitamin D reduced insulin resistance to a small but significant degree, especially in people taking more than 50 mcg (2,000 IU)/day who were vitamin D deficient at baseline, had good glycemic control, were not obese, and were of Middle Eastern ethnicity. However, the supplementation had no significant effects on fasting blood glucose, hemoglobin A1c, or fasting insulin levels.

Clinical trials to date provide little evidence that vitamin D supplementation helps maintain glucose homeostasis, reduces the risk of progression from prediabetes to type 2 diabetes, or helps manage the disease, particularly in vitamin D-replete individuals.

Weight loss

Observational studies indicate that greater body weights are associated with lower vitamin D status, and obese individuals frequently have marginal or deficient circulating 25(OH)D levels [149]. However, clinical trials do not support a cause-and-effect relationship between vitamin D and weight loss.

A systematic review and meta-analysis of 15 weight-loss intervention studies that used caloric restriction, exercise, or both, but not necessarily vitamin D supplementation or other treatments, found that people who lost weight had significantly greater increases in serum 25(OH)D levels than those who maintained their weight [150]. In another study, 10 mcg (400 IU)/day vitamin D and 1,000 mg/day calcium supplementation slightly, but significantly, reduced weight gain amounts in comparison with placebo in postmenopausal women, especially those with a baseline total calcium intake of less than 1,200 mg/day [151]. However, a meta-analysis of 12 vitamin D supplementation trials (including 5 in which body composition measurements were primary outcomes) found that vitamin D supplements without calorie restriction did not affect body weight or fat mass when the results were compared with those of placebo [152].

Overall, the available research suggests that consuming higher amounts of vitamin D or taking vitamin D supplements does not promote weight loss.

Health Risks from Excessive Vitamin D

Excess amounts of vitamin D are toxic. Because vitamin D increases calcium absorption in the gastrointestinal tract, vitamin D toxicity results in marked hypercalcemia (total calcium greater than 11.1 mg/dL, beyond the normal range of 8.4 to 10.2 mg/dL), hypercalciuria, and high serum 25(OH)D levels (typically greater than 375 nmol/l [150 ng/mL]) [153]. Hypercalcemia, in turn, can lead to nausea, vomiting, muscle weakness, neuropsychiatric disturbances, pain, loss of appetite, dehydration, polyuria, excessive thirst, and kidney stones.

In extreme cases, vitamin D toxicity causes renal failure, calcification of soft tissues throughout the body (including in coronary vessels and heart valves), cardiac arrhythmias, and even death. Vitamin D toxicity has been caused by consumption of dietary supplements that contained excessive vitamin D amounts because of manufacturing errors, that were taken inappropriately or in excessive amounts, or that were incorrectly prescribed by physicians, [153-155].

Experts do not believe that excessive sun exposure results in vitamin D toxicity because thermal activation of previtamin D_3 in the skin gives rise to various non-vitamin D forms that limit formation of vitamin D_3. Some vitamin D_3 is also converted to nonactive forms [1]. However, frequent use of tanning beds, which provide artificial UV radiation, can lead to 25(OH)D levels well above 375–500 nmol/L (150–200 ng/mL) [156-158].

The combination of high intakes of calcium (about 2,100 mg/day from food and supplements) with moderate amounts of vitamin D (about 19 mcg [765 IU]/day from food and supplements) increased the risk of kidney stones by 17% over 7 years among 36,282 postmenopausal women who were randomly assigned to take 1,000 mg/day calcium and 10 mcg (400 IU)/day vitamin D or a placebo [159]. However, other, shorter (from 24 weeks to 5 years) clinical trials of vitamin D

supplementation alone or with calcium in adults found greater risks of hypercalcemia and hypercalciuria, but not of kidney stones [160,161].

The FNB established ULs for vitamin D in 2010 (Table 4) [1]. While acknowledging that signs and symptoms of toxicity are unlikely at daily intakes below 250 mcg (10,000 IU), the FNB noted that even vitamin D intakes lower than the ULs might have adverse health effects over time. The FNB recommended avoiding serum 25(OH)D levels above approximately 125–150 nmol/L (50–60 ng/mL), and it found that even lower serum levels (approximately 75–120 nmol/L [30–48 ng/mL]) are associated with increases in rates of all-cause mortality, risk of cancer at some sites (e.g., pancreas), risk of cardiovascular events, and number of falls and fractures among older adults.

Table 4: Tolerable Upper Intake Levels (ULs) for Vitamin D [1]

Age	Male	Female	Pregnancy	Lactation
0-6 months	25 mcg (1,000 IU)	25 mcg (1,000 IU)		
7–12 months	38 mcg (1,500 IU)	38 mcg (1,500 IU)		
1–3 years	63 mcg (2,500 IU)	63 mcg (2,500 IU)		
4–8 years	75 mcg (3,000 IU)	75 mcg (3,000 IU)		
9–18 years	100 mcg (4,000 IU)	100 mcg (4,000 IU)	100 mcg (4,000 IU)	100 mcg (4,000 IU)
19+ years	100 mcg (4,000 IU)	100 mcg (4,000 IU)	100 mcg (4,000 IU)	100 mcg (4,000 IU)

Interactions with Medications

Vitamin D supplements may interact with several types of medications. A few examples are provided below. Individuals taking these and other medications on a regular basis should discuss their vitamin D intakes and status with their healthcare providers.

Orlistat
The weight-loss drug orlistat (Xenical® and alli®), together with a reduced-fat diet, can reduce the absorption of vitamin D from food and supplements, leading to lower 25(OH)D levels [162-165].

Statins
Statin medications reduce cholesterol synthesis. Because endogenous vitamin D is derived from cholesterol, statins may also reduce vitamin D synthesis [165]. In addition, high intakes of vitamin D, especially from supplements, might reduce the potency of atorvastatin (Lipitor®), lovastatin (Altoprev® and Mevacor®), and simvastatin (FloLipid™ and Zocor®), because these statins and vitamin D appear to compete for the same metabolizing enzyme [165-168].

Steroids
Corticosteroid medications, such as prednisone (Deltasone®, Rayos®, and Sterapred®), are often

prescribed to reduce inflammation. These medications can reduce calcium absorption and impair vitamin D metabolism [169-171]. In the NHANES 2001–2006 survey, 25(OH)D deficiency (less than 25 nmol/L [10 ng/mL]) was more than twice as common among children and adults who reported oral steroid use (11%) than in nonusers (5%) [172].

Thiazide diuretics
Thiazide diuretics (e.g., Hygroton®, Lozol®, and Microzide®) decrease urinary calcium excretion. The combination of these diuretics with vitamin D supplements (which increase intestinal calcium absorption) might lead to hypercalcemia, especially among older adults and individuals with compromised renal function or hyperparathyroidism [165,173,174].

Vitamin D and Healthful Diets

The federal government's 2020-2025 *Dietary Guidelines for Americans* notes that "Because foods provide an array of nutrients and other components that have benefits for health, nutritional needs should be met primarily through foods. ... In some cases, fortified foods and dietary supplements are useful when it is not possible otherwise to meet needs for one or more nutrients (e.g., during specific life stages such as pregnancy)."

For more information about building a healthy dietary pattern, refer to the *Dietary Guidelines for Americans (https://www.dietaryguidelines.gov)* and the U.S. Department of Agriculture's *MyPlate. (https://www.choosemyplate.gov/)*

The *Dietary Guidelines for Americans* describes a healthy dietary pattern as one that:

- Includes a variety of vegetables; fruits; grains (at least half whole grains); fat-free and low-fat milk, yogurt, and cheese; and oils.

  Milk, many ready-to-eat cereals, and some brands of yogurt and orange juice are fortified with vitamin D. Cheese naturally contains small amounts of vitamin D. Vitamin D is added to some margarines.

- Includes a variety of protein foods such as lean meats; poultry; eggs; seafood; beans, peas, and lentils; nuts and seeds; and soy products.

  Fatty fish, such as salmon, tuna, and mackerel, are very good sources of vitamin D. Beef liver and egg yolks have small amounts of vitamin D.

- Limits foods and beverages higher in added sugars, saturated fat, and sodium.

- Limits alcoholic beverages.

- Stays within your daily calorie needs.

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