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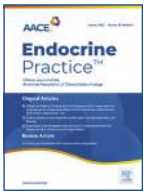

Review Article

Revisiting Vitamin D Guidelines: A Critical Appraisal of the Literature

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ABSTRACT

Background/Objective: The goal of this review is to compare the 2024 and 2011 Endocrine Society's Clinical Practice Guidelines on vitamin D_2 or vitamin D_3 (vitamin D). The 2024 Guideline made recommendations for the general healthy population for skeletal and extra skeletal health benefits of vitamin D. This contrasts with the 2011 Guidelines which provided clinicians with guidance on how to evaluate and treat patients with vitamin D deficiency and prevent recurrence.

Discussion: The 2024 Guideline focused on randomized controlled trials and ignored association studies and other studies that have supported the skeletal and extra skeletal health benefits of vitamin D. The 2024 Guideline recommended empiric vitamin D in children and adolescents aged 1 to 18 years to reduce risk of upper respiratory tract infections, pregnant women to improve pregnancy-related outcomes, prediabetic patients to reduce risk of diabetes, and to improve mortality in those over 75 years.

Conclusion: These guidelines do not apply to individuals with abnormalities in calcium, phosphate, vitamin D, and bone metabolism which were provided in the 2011 Guidelines. For nonpregnant adults up to the age of 75, they recommend the Dietary Reference Intakes of 600 IUs (international units; 1 IU = 25 ng of vitamin D), and 800 IUs as recommended by The Institute of Medicine. Association studies have suggested that to obtain maximum extraskeletal benefits from vitamin D including reducing risk of upper respiratory tract infection for children and adults, autoimmune disorders, pre-eclampsia, low birth weight, neonatal dental caries, and deadly cancers circulating concentrations of 25-hydroxyvitamin D should be at least 30 ng/mL with a preferred range of 40-60 ng/mL as recommended by the 2011 Guidelines.

Introduction

In 2024, the Guideline Development Panel (GDP) for the Endocrine Society published Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline.[1] In the abstract, they acknowledge numerous studies demonstrating associations between serum concentrations of 25-hydroxyvitamin D [25(OH)D] and various health outcomes and concluded that the optimal intake for disease prevention remains uncertain. Therefore, they focused on randomized placebo-controlled trials in general populations. They evaluated the effects of empiric vitamin D_2 or vitamin D_3 (vitamin D) administration (vitamin D intake that exceeds Dietary Reference Intakes [DRIs][2]) throughout life span as well as in select conditions including pregnancy and prediabetes. They acknowledged that empiric vitamin D supplementation may be of value for children and adolescents aged 1 to 18, adults over 75 years of age, those who are pregnant, and those with high-risk prediabetes. They concluded that their recommendations were not meant to replace the current DRIs for vitamin D nor do they apply to people with established indications for vitamin D treatment or testing for circulating concentrations of 25(OH)D.

Perspective

The GDP and the accompanying supporting systematic review addressed 14 clinical questions; 10 of which assessed the effect of vitamin D vs "no vitamin D" in the general population throughout

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; D2d, vitamin d type 2 diabetes trial; DRI, dietary reference intake; IU, international unit; PTH, parathyroid hormone; RCT, randomized controlled trial; VDR, vitamin D receptor; VITAL, VITamin D and Omega A-3 Trial; vitamin D, vitamin D_2 or vitamin D_3.

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the lifespan, during pregnancy and adults with prediabetes.[1,3] The GDP acknowledged that the recommendations were principally based on data obtained from randomized controlled trials (RCTs), systematic reviews and meta-analyses. Heaney[4] and Pilz et al[5] have cautioned the use of nutrient RCTs as the gold standard for interpreting meaningful intervention outcomes. They stressed that nutrient RCTs in general have fundamental differences compared to drug RCTs. For vitamin D RCTs they are often encumbered by the requirement to provide vitamin D supplementation up to the recommended DRI's for age to the placebo group. For studies providing no vitamin D to the placebo group, it is not biologically possible that there is no vitamin D exposure.[4,5] They also note that results from nutrient RCTs can be difficult to interpret because of nutrient–nutrient interactions. A good example being vitamin D and calcium intake, which are not often controlled. Even in studies where calcium is controlled, ie a calcium supplement is provided, it is not possible to know the exact daily calcium intake of any individual due to varying amounts of calcium in the diet which is most often not accounted for. It is also now recognized that individuals who took the same dose of vitamin D and raised their circulating concentrations of 25(OH)D to the same level that gene expression analysis of peripheral blood mononuclear cells revealed that approximately 60% had a robust gene expression response while the other 40% had a much-decreased response. This is another variable that can make vitamin D RCTs difficult to interpret.[6,7] The GDP ignored association studies and other biochemical, histologic, and pathologic studies. Ignoring such studies can have long-term dire consequences. Semmelweis in the 1840s promoted hand-washing with chlorine water to dramatically improve maternal and infant survival after delivery. This simple recommendation based on his association studies was not only ignored but vigorously opposed by the established medical community. It was concluded that this idea was insane, and it was necessary to silence him. His colleagues alleged he had a nervous breakdown and committed him to insane asylum. Those that committed him wanted to emphasize their disdain for promoting this crazy idea by having the guards bludgeon him upon his arrival resulting in a gangrenous wound that led to his death 2 weeks later.[8] In 1822, Sniadecki observed that children in Warsaw were at high risk for developing rickets whereas children living in the rural areas had little evidence for this crippling bone deforming disease. He made the association that it was lack of sun exposure in the inner city of Warsaw that was the cause of rickets.[9] A hundred years would pass before it was demonstrated that direct sun exposure could prevent and cure rickets.[10] The number of children harmed in the ensuing 100 years by ignoring this simple association observation throughout the world is incalculable.

Association and Other Studies Supporting the Maintenance of Serum Concentrations of 25-hydroxyvitamin D of at Least 30 ng/mL for Maximum Health

Bone Health

The GDP acknowledged that vitamin D plays an important role in peak bone mass accrual for the age span of 18 to 50 years, which is important for reducing risk of osteoporotic fractures later in life. The GDP recognized that 24%, 22%, and 24% of adults 18-50, 40-59, and 60 years and older in the United States have a circulating concentration of 25(OH)D < 20 ng/mL (low vitamin D status), respectively. In Europe, population-based data showed approximately 40% of children and adults have a low vitamin D status.[1] The panel concluded based on recent clinical trials including the VITamin D and Omega A-3 Trial (VITAL) RCT[11,12] that reported that vitamin D intake of 2000 international units (IU; one IU = 25 ng of vitamin D) daily in men 50 years and older and women 55 years and older for up to 5 years did not reduce risk for fracture or improve BMD. Therefore, there was no need to recommend empiric vitamin D supplementation in this age group for the maintenance of maximum bone health. They recommended the DRI of 600 and 800 IUs daily for children 1 year and older, and adults up to the age of 70 years and adults 70 years and older respectively, as recommended by the Institute of Medicine (IOM).[2] This amount of vitamin D from the diet was all that was required to maintain a circulating concentration of 25(OH)D of 20 ng/mL which is adequate for maximum bone health. They also recommended there was no need for screening vitamin D status in these age groups.[1]

Vitamin D's priority function for health is to maintain serum calcium concentrations in a physiologically acceptable range to maintain cellular metabolic functions including signal transduction, neuromuscular and cardiac function among the many other activities.[13] Vitamin D accomplishes this by increasing the efficiency of intestinal calcium absorption of dietary calcium. When there is inadequate dietary calcium to satisfy the body's requirement, vitamin D through its active form, 1,25-dihydroxyvitamin D, increases the removal of calcium from the skeleton via the receptor activator of NF kappa B ligand increasing numbers of osteoclasts to release calcium into the extracellular space and remove the matrix that was associated with it. The decrease in ionized calcium associated with vitamin D deficiency results in an increase in the production and release of parathyroid hormone (PTH).[13] Among its many functions, PTH increases numbers of osteoclasts to remove calcium and matrix from the skeleton. It also results in phosphate wasting in the kidneys reducing serum phosphate concentrations. An inadequate calcium-phosphate product causes the inability of newly laid down collagen matrix from being mineralized. In children, this can cause rickets and in adults, osteomalacia.[14-16] Therefore, vitamin D deficiency causes two insults to the skeleton. It reduces bone mineral density and prevents bone mineralization. (Fig. 1) What vitamin D cannot do is make a new bone.[16] Therefore, vitamin D cannot treat osteoporosis. It cannot improve BMD with one exception. Correction of vitamin D deficiency and secondary hyperparathyroidism can improve the circulating calcium-

Highlights

- Perspective of 2024 Endocrine Society's Guidelines on Vitamin D compared to and contrasted to the 2011 Endocrine Society's Guidelines
- Reviewed the 2024 Guidelnes Vitamin D for the Prevention of Disease: For public health and extra skeletal health
- Reviewed associations', and other studies that support a serum concentration of 25-hydroxyvitamin D of at least 30 ng/mL, for bone health and extra skeletal health benefits
- How much vitamin D is required to maintain a 25-hydroxyvitamin D in the preferred range of 40-60 ng/mL for maximum health.

Clinical Relevance

This review compares and contrasts the 2024 Endocrine Practice Guidelines on Vitamin D with the 2011 Endocrine Practice Guidelines. It provides guidance for the evaluation, treatment, and prevention of vitamin D deficiency for skeletal and nonskeletal health and maintaining a circulating concentration of 25-hydroxyvitamin D of at least 30 ng/mL.

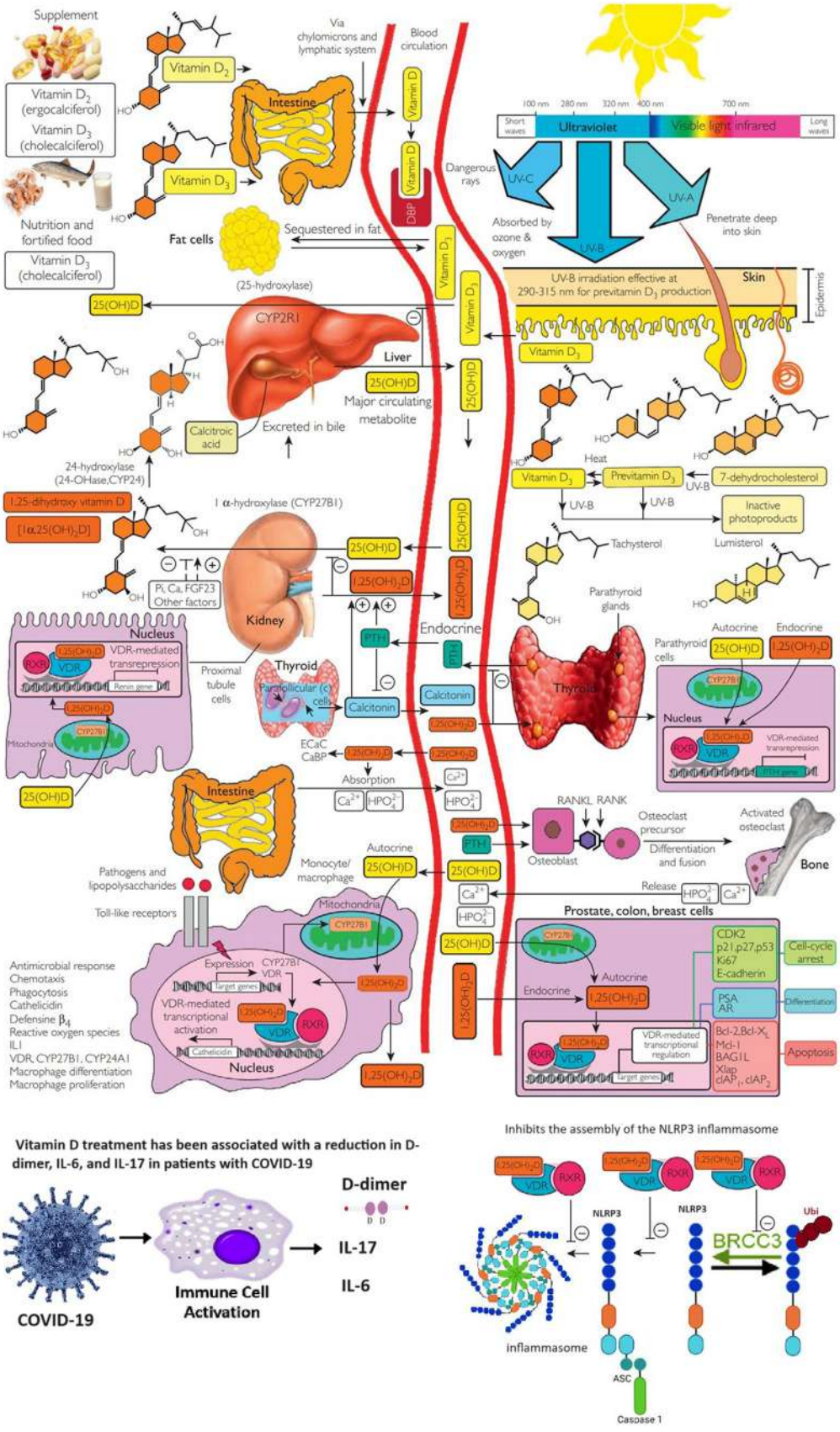

Fig. 1. Schematic representation of the synthesis and metabolism of vitamin D for skeletal and nonskeletal function. *1-OHase* = 25-hydroxyvitamin D-1a-hydroxylase; *24-OHase* = 25-hydroxyvitamin D-24-hydroxylase; *25(OH)D* = 25-hydroxyvitamin D; *1,25(OH)$_2$D* = 1,25-dihydroxyvitamin D; *BRCC3* = deubiquitinase; *CaBP* = calcium-binding protein; *CYP27B1* = Cytochrome P450-27B1; *DBP* = vitaminD- binding protein; *ECaC* = epithelial calcium channel; *FGF-23* = fibroblast growth factor-23; *IL-16* = interleukin-6; *IL-17* =

phosphate product as a result promoting the deposition of calcium hydroxyapatite into unmineralized matrix and by doing so increasing BMD thereby reducing risk for fracture. A good example was the demonstration of a 52.8% increase in BMD in the lumbar spine and 27.1% increase at the forearm in a patient with an initial serum concentration of 25(OH)D < 5 ng/mL and after 2 years of vitamin D therapy.[15] This was a result of improvement in her calcium and phosphate metabolism, thereby re-establishing an adequate calcium-phosphate product for the passive mineralization of unmineralized bone matrix.[15]

In contrast to the 2024 Guidelines[1], in which the goal was to establish clinical guidelines for the use of vitamin D to lower the risk of disease in individuals without established indications for vitamin D treatment or 25(OH)D testing, the 2011 Endocrine Practice Guidelines on Vitamin D[17] purpose was to provide guidance to evaluate, prevent and treat vitamin D deficiency. They placed an emphasis on the care of patients who are at risk for vitamin D deficiency and insufficiency, defined as circulating concentrations of 25(OH)D < 20 ng/mL and 21-29 ng/mL respectively.[17] The 2011 Guidelines took into consideration several studies that related circulating concentrations of 25(OH)D to markers of bone metabolism including PTH. Chapuy et al[18] recognized the indirect association between PTH and 25(OH)D whereby PTH serum concentrations began to plateau at around 30-40 ng/mL. Similar observations were made by Holick et al[19] and Thomas et al.[20] (Fig. 2 *A*). Holick et al[19] reported that elderly women had 3 times lower risk of having secondary hyperparathyroidism if their circulating concentration of 25(OH)D was greater than 30 ng/mL when compared to being less than 20 ng/mL. A study of 3.8 million serum concentrations of 25(OH)D related season in the United States with serum concentrations of PTH demonstrated a dramatic seasonal influence.[21] The nadir circulating concentration of 25(OH)D occurred at the end of the winter and was approximately 18 ng/mL compared to the end of summer which was approximately 29 ng/mL in both Northern and Central states. The serum PTH concentrations were indirectly associated with serum concentrations of 25(OH)D. When serum 25(OH)D was at its nadir, 4 weeks later PTH was at its peak concentration. At the end of the summer when the 25(OH)D concentrations were at their peak, 4 weeks later the PTH concentrations were at their nadir.[21] (Fig. 2 *B*) These data demonstrate the intimate relationship that PTH has with serum concentrations of 25(OH)D and further substantiates the indirect association of PTH with 25(OH)D concentrations.[18-20] What the consequences of the cyclical rise and fall of PTH on the skeleton is not fully understood. However, PTH does increase osteoclastic activity that potentially would increase removal of mineral and matrix from the skeleton and decrease serum phosphate concentrations thereby increasing risk for decreased BMD and rickets/osteomalacia. In 2010, Priemel et al[22] made a remarkable observation relating serum concentrations of 25(OH)D with risk for osteomalacia. They collected iliac crest bone biopsies and circulating concentrations of 25(OH)D in 675 healthy adults who died prematurely due to an accident such as a motor vehicle accident. The age range was 20-90+ years. They reported that the bone biopsies revealed that 26.5% had evidence of osteomalacia and 36.1% had evidence for osteoidosis (buried unmineralized matrix within the mineralized bone). The authors concluded that they observed no evidence of osteomalacia present in bone biopsies when circulating concentrations of 25(OH)D were at least 30 ng/mL. A plot of osteoid volume/bone volume with 25(OH)D revealed 22% of the adults with a circulating concentration of 25(OH)D of between 21 and 29 ng/mL had evidence of osteomalacia. (Fig. 2 *C*). The VITAL trial evaluated the effect of 2000 IUs vitamin D_3 daily for a median follow-up of 5.3 years on BMD and fracture reduction and concluded that there was no benefit.[12] The authors acknowledged that the mean serum concentration of 25(OH)D in 16,757 participants was 30.7 ± 10 ng/mL. 64% of the participants had a circulating concentration of 25(OH)D > 30 ng/mL and 12.9% and 2.4% were < 20 ng/mL and < 12 ng/mL, respectively. The "placebo" group was permitted to take up to 800 IUs vitamin D daily. Typically supplement manufacturers add at least 20% and up to 50% more active ingredients in their supplements to maintain shelf life. Therefore, the so-called "placebo" group may have been taking as much as 1000-1200 IUs daily. This would help explain why 64.7% of the participants had a circulating concentration of 25(OH)D > 30 ng/mL at baseline. They reported that 401 subjects who had a circulating concentration of 25(OH)D less than 12 ng/mL at baseline, had 7 fractures in the vitamin D group, and 8 in the placebo group. They then evaluated fractures in the other 16,356 participants and found 561 fractures in the vitamin D treated group compared to 577 fractures in the "placebo" group. There was no statistically significant difference, but this is not unexpected since less than 13% of the subjects were vitamin D deficient [25(OH)D less than 20 ng/mL]. This study highlights the need, at a minimum, to enroll subjects who have a baseline serum concentration of 25(OH)D that is considered to be deficient if there is any possibility of observing a beneficial outcome of vitamin D supplementation.[4,5]

In Utero, Pregnancy, and Neonatal Health

The GDP concluded although there was no statistically significant difference for pre-eclampsia, gestational hypertension, intrauterine mortality, neonatal mortality, preterm birth, or small for gestational age births; however, absolute risk differences suggested potential important benefit for all outcomes. In their conclusion, they suggest potential benefit of empiric vitamin D in pregnant women and that 25(OH)D testing is not recommended. Their systematic review suggested clinical benefit in dosages ranging from 600 IUs to 5000 IUs with a weighted average of approximately 2500 IUs per day.

Pre-eclampsia

Association studies provided the first insight of the association of vitamin D status with risk for pre-eclampsia. Bodnar et al[23] reported on the effect of maternal 25(OH)D concentrations on risk of pre-eclampsia. It was a nested case-controlled study of pregnant nulliparous women followed from less than 16-week gestation to delivery. The main outcome measure was pre-eclampsia (new-onset gestational hypertension and proteinuria for the first time after 20-week gestation). Adjusted serum 25(OH)D concentrations were lower in women who subsequently developed pre-eclampsia compared with controls. There was a monotonic dose-response relation between serum 25(OH)D at less than 26 weeks and risk of pre-eclampsia. After confounder adjustment, a 20 ng/mL decline in 25(OH)D concentration doubled the risk of pre-eclampsia. (Fig. 2 *D*) A systematic review of 8 relevant publications revealed an overall significant association between vitamin D deficiency and risk for pre-eclampsia. In the subgroup analysis circulating concentrations of 25(OH)D < 20 ng/mL revealed a significant relationship between vitamin D deficiency and increased risk for pre-eclampsia.[32] An evaluation of the effect of vitamin D supplementation (4400 IUs vs 400 IUs/day) initiated in early pregnancy (10-18 weeks) revealed

interleukin-17; *NLRP3* = NOD-, LRR- and pyrin domain-containing protein 3; *Ubi* = ubiquitin; *PTH* = parathyroid hormone; *RANK* = receptor activator of the NF-kB; *RANKL* = receptor activator of the NF-kB ligand; *RXR* = retinoic acid receptor; *TLR2/1* = Toll-like receptor 2/1; *VDR* = vitamin D receptor; *vitamin D* = vitamin D_2 or vitamin D_3.

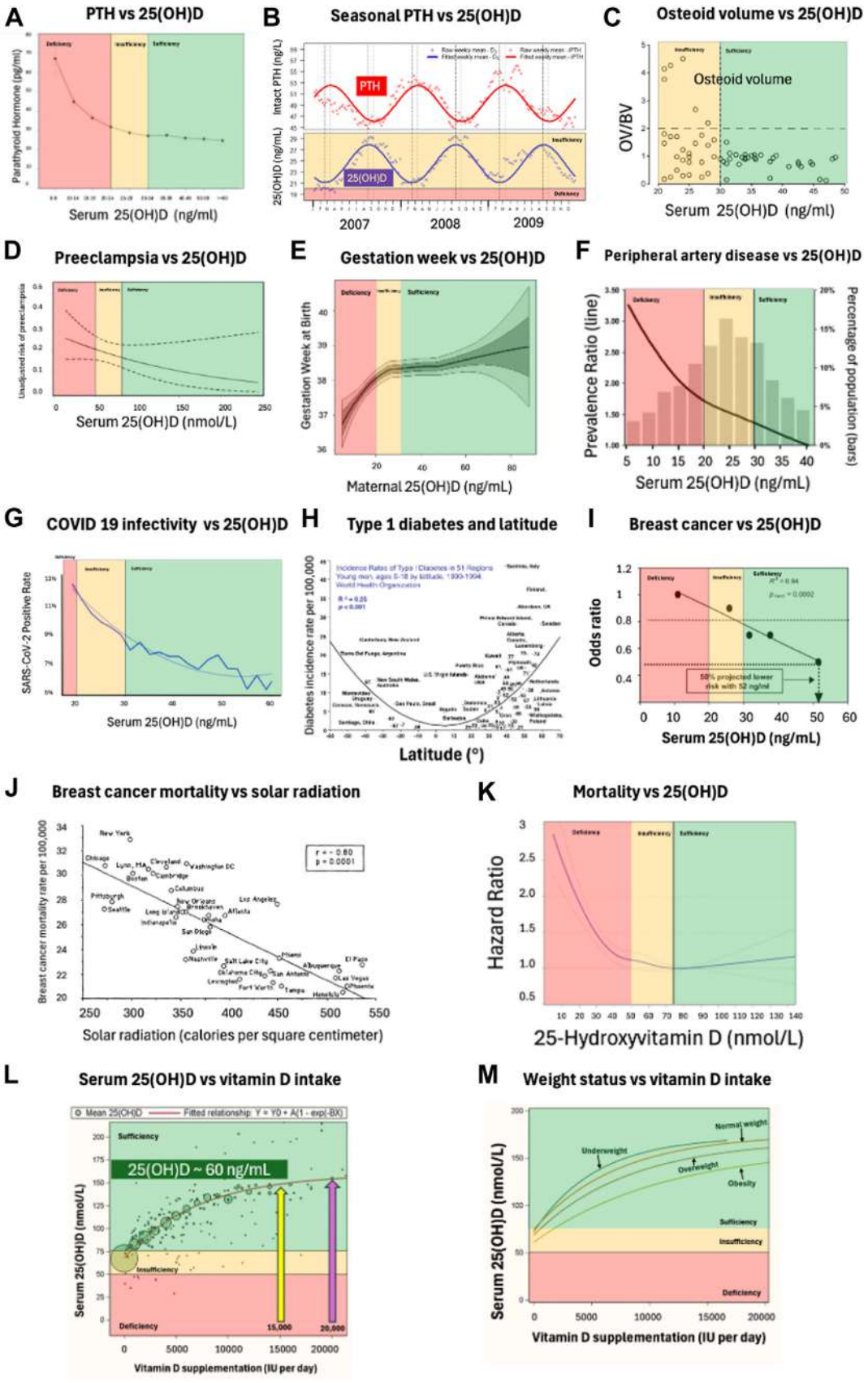

Fig. 2. Association studies relating circulating concentrations of 25(OH)D to various outcome measures. Details of the figures can be found in the original publication. *A*, PTH related to serum concentrations of 25(OH)D with permission,[19] *B*, Seasonal variation in serum concentrations of 25(OH)D and PTH with[21] open access, *C*, Osteomalacia measured as osteoid volume/bone volume with permission,[22] *D*, Pre-eclampsia related to serum concentrations of 25(OH)D with permission,[23] *E*, Gestational week at birth related to serum

there was no significant difference between treatment (N = 408) or control (N = 408) and the incidence of pre-eclampsia. However, in a cohort analysis and after adjustment of cofounders, a significant effect of vitamin D status [25(OH)D >_30 ng/mL] was reported in both early and late pregnancy compared to 25(OH)D < 30 ng/mL. Most importantly, differential expression of 348 vitamin D-associated genes was found in peripheral blood of women who developed pre-eclampsia.[33] Functional enrichment and network analysis suggested several highly functional modules related to systemic inflammatory and immune responses, including some nodes with a high degree of connectivity. This study may be giving an insight why interventional studies often do not provide the anticipated outcome based on association studies. In this case maintenance of a serum concentration of 25(OH)D of at least 30 ng/mL before as well as during pregnancy maximizes the immune system to reduce risk for pre-eclampsia. It is also possible that introducing vitamin D supplementation, whether it be 4400 IUs or 400 IUs daily, early in pregnancy is still influencing some of the same vitamin D-responsive genes thereby attenuating risk for pre-eclampsia in the control group. Pre-eclampsia, which affects approximately 4-5% of pregnancies in the United States, is associated with significant maternal and neonatal morbidity and mortality and therefore recommending vitamin D testing and vitamin D supplementation above the DRI for all pregnant women is warranted.

Premature Births

McDonnell et al[24] evaluated the incidence of premature births in pregnant patients aged 18-45 years and related them to circulating concentrations of 25(OH)D at the first prenatal visit. Free vitamin D supplements were offered. The treatment goal was to improve circulating concentrations of 25(OH)D to be greater than or equal 40 ng/mL. Of the 1064 participants, the overall preterm birth rate was 13%. The LOESS curve demonstrated a direct relationship between serum concentrations of 25(OH)D and age. (Fig. 2 *E*) Women who had a serum concentration of 25(OH)D greater or equal to 40 ng/mL had a 62% lower risk of preterm births.

Cesarean Section

Cesarean birth rate continues to increase globally. Currently more than 30% births in the United States require cesarean section. An evaluation of 253 women of whom 43 had a primary cesarean revealed an inverse association with serum concentrations of 25(OH)D. It was observed that women with a serum concentration of < 15 ng/mL were 50% more likely to require a cesarean section vs vaginal delivery compared to women who had a circulating concentration of 25(OH)D > 15 ng/mL. The benefit for reduced risk was observed for women who had increasing serum concentrations of 25(OH)D up to 60 ng/mL with the highest serum 25(OH)D at the lowest probability of requiring a cesarean section. A multivariate logistic regression analysis controlling for race, age, education level, insurance status, maternal birthplace and alcohol use revealed women with vitamin D deficiency < 15 ng/mL were almost four times more likely to have a primary cesarean section.[34]

Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment

Rostami et al[35] conducted a study to evaluate the effect of prescreening pregnant women for their vitamin D status and the effect of vitamin D supplementation on pregnancy and birth outcomes. They conducted the randomized controlled study at health centers in 2 cities in Iran. One city was designated for prescreening pregnant women for serum concentrations of 25(OH)D while pregnant women in the other city were not prescreened. Women with severe deficiency, 25(OH)D < 10 ng/mL, received more vitamin D supplementation orally and intramuscularly compared to women with moderate deficiency, 25(OH)D 10-20 ng/mL. Fifty-three percent of the women who were screened and received vitamin D supplementation achieved a serum concentration of 25(OH)D > 20 ng/mL compared to only 2% of women in the nonscreened group who did not receive vitamin D supplementation. Adverse pregnancy outcomes including preeclampsia, gestational diabetes and preterm delivery were decreased by 60%, 50%, and 40%, respectively, in women who were screened and received vitamin D supplementation based on their baseline serum concentration of 25(OH)D.

Infant Dental Caries

Dental caries is the most common chronic disease of childhood. Primary teeth begin to develop in utero and there is evidence that prenatal influences including vitamin D status affect the integrity of the enamel and subsequent resistance to decay. Schroth et al[36] conducted a prospective cohort study of expected mothers and related their serum circulating concentration of 25(OH)D with a dental exam of their 1-year-old child. They observed an inverse relationship with early childhood caries and maternal prenatal serum concentrations of 25(OH)D. Infant risk for dental caries was reduced by 70% if their mother had a prenatal serum concentration of 25(OH)D of at least 40 ng/mL.

Type 2 Diabetes

In 2004, Scragg et al[37] performed an analysis of data from participants who participated in the Third National Health and Nutrition Examination Survey (1988-1994). The serum concentrations of 25(OH)D in this cross-sectional survey of 6228 people were related to fasting and 2-hour plasma glucose and serum insulin measurements. It was concluded that there was an inverse association between vitamin D status and diabetes, possibly involving insulin resistance. Observations that beta islet cells have a vitamin D receptor (VDR) and $1,25(OH)_2D_3$ influences insulin secretion and sensitivity fueled multiple clinical trials to determine if improvement in vitamin D status reduced risk of type 2 diabetes with mixed results.[38] A seminal study known as the vitamin d type 2 diabetes trial (D2d) RCT evaluated randomly assigned 2423 adults who had evidence for pretype 2 diabetes to either 4400 IUs vitamin D_3 in a soft gel pill daily or a placebo soft gel pill for a median follow-up of 2.5 years.[39] After 2 years, serum concentrations of 25(OH)D increased from 27.7 ng/mL to 54.3 ng/mL in the vitamin D treated group compared to no significant change in the placebo group (28.2 ng/mL at baseline and 28.8 ng/mL after 2 years). It was concluded that among these participants who were at high risk for type 2 diabetes not selective for vitamin D insufficiency, that vitamin D supplementation did not significantly reduce risk of type 2 diabetes compared to the placebo group. However, like the VITAL trial,[11] where 12.9% of the participants had a circulating concentration of 25(OH)D < 20 ng/mL, only 22.8% in the treatment group and 20.6% in the placebo group were vitamin D deficient at baseline in the D2d trial. Although the trial provided a placebo gel capsule, the participants were encouraged to meet the Institute of Medicine's recommended amounts of supplemental vitamin D for their age

concentrations of 25(OH)D with permission,[24] *F*, Peripheral Artery Disease associated serum concentrations of 25(OH)D with permission,[25] *G*, COVID infectivity related to serum concentrations of 25(OH)D open access,[26] *H*, Latitude associated with incidence of type 1 diabetes with permission,[27] *I*, Breast cancer incidence associated with serum concentrations of 25(OH)D with permission,[28] *J*, Geographic variation in breast cancer mortality and exposure to solar radiation with permission,[29] *K*, All-cause mortality related to serum concentrations of 25(OH)D with permission,[30] *L*, Serum concentrations of 25(OH)D associated with vitamin D supplementation open access, and [31] *M*, Serum concentrations of 25(OH)D associated with vitamin D supplementation related to underweight, normal weight, and overweight open access.[31]

(600 or 800 IUs/day). A posthoc analysis in a subgroup of participants with a baseline serum concentration of 25(OH)D < 12 ng/mL revealed that the vitamin D treatment group showed a significant 62% reduction in risk of developing type 2 diabetes compared to the placebo group. An evaluation of intra-trial exposure to vitamin D and new onset diabetes among the study participants in the D2d trial revealed that the hazard ratios for diabetes among the participants treated with vitamin D and who maintained serum concentrations of 25(OH)D of 100-124 nmol/L (40-49 ng/mL) and greater than or equal to 125 nmol/L (50 ng/mL) were 0.48 (0.29-0.80) and 0.29 (0.17-0.50), respectively compared with those who maintained a level of 50-74 nmol/L (20-29 ng/mL).[40] This observation confirms a previous meta-analysis reporting that participants in the vitamin D treatment group reduce relative risk of type 2 diabetes by 15%. However, remarkably participants who were assigned to the vitamin D supplement and maintained a serum concentration of 25OH)D of at least 50 ng/mL compared with 20-29 ng/mL during follow-up, reduced risk of diabetes by 76% with a 3-year absolute risk reduction of 18.1%.[41] Vitamin D treatment increased likelihood of regression to normal glucose regulation by 30% and there were no significant adverse events including kidney stones, hypercalciuria or hypercalcemia.

Cardiovascular Disease

In 2008, Melamed et al[25] reported on the prevalence of peripheral artery disease (PAD) in 4839 participants of the National Health and Nutrition Examination Survey III as related to serum concentrations of 25(OH)D. They observed that when comparing circulating concentrations of 25(OH)D < 17.8 ng/mL compared to > 29.2 ng/mL the prevalence of PAD was reduced by 80%. (Fig. 2 *F*) Furthermore, for each 10 ng/mL lower 25(OH)D serum concentration, the multivariable-adjusted prevalence ratio of PAD was 1.35 (95% confidence interval: 1.15, 1.59). This observation was supported by studies demonstrating that vitamin D's effect on regulating blood pressure and various cardiovascular functions.[42-44] Dong et al[45] reported a randomized controlled trial of 49 normotensive African American teens with a baseline serum concentration of 25(OH)D of 13 ng/mL who received either 400 IUs or 2000 IUs vitamin D_3 daily for 16 weeks. The teenagers receiving 2000 IUs vitamin D_3 daily and raised their serum concentration of 25(OH)D to 34 ng/mL, had a significant decrease in carotid-femoral arterial wall stiffness measured by pulse wave velocity. This was compared to a significant increase in arterial wall stiffness in the teenagers receiving 400 IUs of vitamin D_3 daily. They had increased their circulating concentration of 25(OH)D to only 24 ng/mL. Raed et al[46] conducted a randomized trial evaluating monthly doses that were equivalent to ~600IUs, 2000 IUs, or ~4000 IUs daily for 16 weeks in 49 overweight African American teenagers and adults (ages 13-45 years) who had a circulating concentration of 25(OH)D < 20 ng/mL. They observed a significant dose dependent improvement in arterial vascular blood flow for both carotid-femoral and carotid-radial pulse wave velocity. Kumar et al[47] conducted a randomized controlled trial in 120 nondiabetic women and men with a baseline serum concentration of 25(OH)D of 13 ng/mL with chronic kidney disease (stage 3-4) and who received either placebo or 300,000 IUs vitamin D_3 twice during the 16-week study to evaluate endothelial function and brachial artery flow. Patients who took the vitamin D supplement and increased their circulating concentration of 25(OH)D by 23.4 ng/mL had a significant increase in their endothelial-dependent brachial artery flow. The placebo group did not show any improvement. Several clinical trials were initiated to determine the health benefit of vitamin D supplementation. The results were mixed. Acharya et al[48] evaluated the effects of nontreatment and vitamin D treatment in 20,025 vitamin D deficient patients without a prior history of a myocardial infarction (MI). They observed that those patients who were treated with vitamin D and maintained a circulating concentration of 25(OH)D ≥ 30 ng/mL had significantly lower risk for an MI compared to the patients treated with vitamin D and maintained a circulating concentration of 25(OH)D of 21-29 ng/mL and the untreated patients with serum concentrations of ≤ 20 ng/mL. There was no difference in the risk of MI between the untreated patients and patients who maintained a circulating concentration of 25(OH)D of 21-29 ng/mL. Both treatment groups had a significantly lower all-cause mortality compared to the untreated patients. The VITAL study[11] where 64.7% were vitamin D sufficient [25OH)D > 30 ng/mL] concluded that 2000 IUs vitamin D_3 daily had no benefit for cardiovascular health; a not unexpected result in light of the previous observation.[48]

Infectious Diseases

The GDP recommended in Recommendation 1 that children and adolescents should receive empiric vitamin D supplementation (estimated weighted average was approximately 1200 IUs daily) to potentially lower the risk of respiratory tract infections. The GDP in reviewing the literature ignored what is now one of the most common respiratory infections in children and adults, COVID 19. In a study of 191,779 patients in the United States it was observed that the SARS-CoV-2 positivity rate was inversely related to serum concentrations of 25(OH)D.[26] There was a 54% reduced risk of COVID infection for patients who had a serum concentration of 25(OH)D of 34 ng/mL compared to those patients with concentrations < 20 ng/mL. The positivity rate continued to decline for patients having increasing concentrations of 25(OH)D to 60 ng/mL.[26] (Fig. 2 *G*) An evaluation of vitamin D status in 4599 veterans hospitalized with a positive SARS-COVID-2 test revealed increased serum concentrations of 25(OH)D in a continuous manner from 15-60 ng/mL was independently associated with COVID 19-related decrease in hospitalizations (22%) and mortality (45%).[49] A similar observation was made in 287 patients in a Boston hospital. The overall decreased odds of death was 66%, acute respiratory distress syndrome 78%, and severe sepsis/septic shock 74% if the patient arrived at the hospital with a serum concentration of 25(OH)D of at least 30 ng/mL.[50] The authors also reported that this benefit was only observed in normal weight patients. Villasis-Keever et al[51] reported a multicenter double-blind placebo-controlled intention-to-treat trial to investigate the efficacy and safety of vitamin D supplementation to prevent COVID 19 in front line health care workers who were caring for COVID 19 hospitalized patients. The health care workers were randomly assigned to either 4000 IUs vitamin D_3 daily for 30 days or a placebo. Those health care workers taking vitamin D supplementation had a 74% significantly lower infection rate (6.4% compared to 24.5% in the placebo group) and 77% lower risk of acquiring the infection. Similarly, Rostogi et al[52] conducted a randomized placebo-controlled trial to determine the effect of high-dose, oral vitamin D_3 on SARS-CoV-2 viral clearance in asymptomatic or mildly symptomatic SARS-CoV-2 positive vitamin D deficient [25(OH)D < 20 ng/mL] patients. Forty participants were randomized and either received 60,000 IUs vitamin D_3 or a placebo daily for 7 days. Circulating concentrations markedly increased from a baseline of 8.6 ng/mL to more than 50 ng/mL in some of the patients receiving the vitamin D supplementation whereas the placebo group had a baseline of 9.5 ng/mL that did not significantly change up to 15.2 ng/mL. 62.5% of the participants receiving vitamin D supplementation became SARS-CoV-2 RNA negative, whereas only 20.8% became negative in the placebo group.

Autoimmune Disorders

In the 1970s, there was an appreciation that inactive T lymphocytes and B lymphocytes when activated developed a VDR. When activated T and B lymphocytes were exposed to $1,25(OH)_2D_3$,

the hormone had a dramatic influence on the regulation and expression of cytokines and antibodies respectively.[13,53,54] Epidemiologic studies demonstrated a higher prevalence for multiple sclerosis (MS) and type 1 diabetes at higher latitudes (Fig. 2 *H*)[27] that appeared to be associated with decreased exposure to sunlight and therefore vitamin D production.[27,53] The Nurse's Health Study of more than 187,000 women revealed that women had the highest intake of dietary vitamin D (approximately 700 IUs/day) had a 33% lower incidence of MS compared to those with a lower intake. Women who took at least 400 IUs daily had a 41% reduced risk of developing MS compared to nonusers.[55] An evaluation of vitamin D status of 7 million US military personnel revealed that they were 62% lower risk of developing MS if their serum concentration of 25(OH)D was greater than 40 ng/mL.[56] There is also an association between perinatal and neonatal vitamin D status and risk for MS. Offsprings of moms whose circulating concentrations of 25(OH)D were less than 12 ng/mL had a 90% higher risk of developing MS compared to offspring of mothers with a serum concentration of 25(OH)D of at least 15 ng/mL. Neonates with a serum concentration of 25(OH)D < 8 ng/mL compared to neonates with 25(OH)D of at least 20 ng/mL at a 47% higher risk of developing MS later in life.[57] Neonatal vitamin D deficiency is also associated with increased risk for type 1 diabetes. A birth cohort study in northern Finland reported that children during their first year of life who received the recommended 2000 IUs vitamin D_3 daily reduce their risk of developing type 1 diabetes by 88%.[58] A subgroup analysis of the VITAL trial[59] revealed after a median of 5.3 years of receiving 2000 IUs vitamin D_3/day reduced the rate of autoimmune diseases by 22%. When only the last 3 years of the intervention was considered, the group receiving 2000 IUs vitamin D_3 daily had 39% fewer participants with confirmed autoimmune disease than the placebo group. Subjects in the vitamin D group after 1 year raised their serum concentration of 25(OH)D from 29.8 ng/mL to 41.8 /mL while the group considered placebo changed minimally. A follow-up study to determine whether the initial 2000 IUs vitamin D_3/day continued to reduce risk of developing an autoimmune disease after stopping the vitamin D supplementation for 2 years revealed the beneficial effect dissipated and that those observed for more than 2 years developed confirmed autoimmune disease compared to the placebo group.[60]

Cancer

In 1936, Peller et al[61] associated outdoor occupations in which less lethal skin cancer was increased while other more lethal cancers of the organs were diminished. He reported the United States Navy skin cancer rate was eight times that found among men of the same age range in the general population. The total rate of more deadly cancers of other organs in the navy personnel was reduced by 40% of the expected rate.[61] In 1941, Apperly associated latitude in the United States and Canada with risk of cancer and concluded that the general cancer rate declines with increasing solar radiation ie living at lower latitudes.[62] In 1980, Garland and Garland[63] reported that colon cancer mortality rates in the US were highest in places where populations were exposed to the least amount of natural sunlight. They hypothesized that decreased sun exposure was associated with reduced production of vitamin D and concluded that vitamin D deficiency could be a major factor in colon cancer mortality rates.[63] A follow-up study in 1990 reported that the risk of fatal breast cancer was inversely proportional to intensity of local sunlight.[29] To confirm their hypothesis, Garland et al[64] investigated the relationship of serum concentrations of 25(OH)D with subsequent risk of colon cancer in an 8 year prospective study. They observed risk of colon cancer was reduced by 75% in subjects who had a circulating concentration of 25(OH)D of between 27 and 32 ng/mL and 80% reduction for those with circulating concentration of 25(OH)D of 33-41 ng/mL compared to patients with a circulating concentration of 25(OH)D of between 4 and 19 ng/mL. A pooled analysis with 1760 individuals relating serum concentrations of 25(OH)D with risk for breast cancer revealed individuals with a serum concentration of 25(OH)D of approximately 52 ng/mL had a 50% lower risk of breast cancer than those with a serum concentration < 13 ng/mL.[28] (Fig. 2 *I*) This analysis supported the geographical variation in breast cancer mortality in the United States.[29] (Fig. 2 *J*) These insightful observations were confirmed by a multitude of other studies relating decreased sun exposure and vitamin D deficiency with increased risk for as many as 12 different cancers.[65] A meta-analysis of 10 randomized controlled trials concluded that vitamin D supplementation significantly reduced total cancer mortality but did not reduced total cancer incidence.[66] The VITAL trial reported the rate of death from cancer excluding the first 2 years of follow-up was 25% lower in the group that received 2000 IUs vitamin D_3 daily compared to the placebo group.[11] A secondary analysis of the VITAL randomized controlled trial revealed that supplementation with 2000 IUs vitamin D_3 daily significantly reduced incidence of metastatic and fatal cancer by 38% in the participants who had a BMI < 25. There was no benefit to those with a BMI greater than 30.[67] In 2019 Urashima et al[68] reported results of a randomized double-blind placebo-controlled clinical trial that evaluated the efficacy of 4000 IUs vitamin D_3 daily compared to the control group who received 400 IUs vitamin D_3 daily for up to 8 years on relapse-free survival of patients with cancers of the digestive track and found no benefit. The median serum concentration of 25(OH)D at baseline was 16.1 ng/mL for the vitamin D treatment group receiving 2000 IUs daily and 18.7 ng/mL for the group receiving 400 IUs vitamin D daily. At the end of the trial, the circulating concentration of 25(OH)D for the patients who received 4000 IUs daily compared to the group receiving 400 IUs daily of vitamin D was 34.8 ng/mL compared to 18.7 ng/mL respectively. The results confirmed what the naysayers have been saying about the lack of efficacy of vitamin D related to cancer mortality. In 2023, Kanno et al[69] reported a posthoc subgroup analysis of this study relating detectable p53 antibodies in the serum and nuclear accumulation of p53 by immunohistochemistry in more than 99% of cancer cells present in pathology specimens. They concluded that patients who had detectable serum anti-p53 antibody and received 2000 IUs daily had a significant, more than 2.5-fold improvement in relapse or death compared to the placebo group that had undetectable p53 immunoreactivity. This study reiterates the importance of understanding mechanisms of action as it relates to the role of vitamin D in reducing risk for cancer and cancer mortality. In the 1980s, we began to appreciate some of the noncalcemic mechanisms of action that $1,25(OH)_2D_3$ could initiate in a variety of cells not related to calcium metabolism including keratinocytes, colon, prostate, and breast cells as well as malignant cells including leukemia, breast, colorectal, and prostate cancer.[70] For normal cells that contained a VDR, $1,25(OH)_2D_3$ was found to be extremely effective in regulating more than 1000 genes responsible for controlling innate and adaptive immunity, cell growth by inducing cellular differentiation, and decreasing proliferation.[6,70,71] (Fig. 1) The anti-proliferative and pro-differentiation properties were found to be effective in treating the hyperproliferative skin disorder psoriasis.[53,70] Research over the past 4 decades has revealed the multifaceted actions of $1,25(OH)_2D_3$ in maintaining cellular health. As part of its armamentarium, $1,25(OH)_2D_3$ can induce apoptosis and deprive malignant cells of nutrition by decreasing angiogenesis to the developing cancer. In addition, it can affect the innate and adaptive immune systems to decrease the production of cytokines promoting cell

growth and enhancing production of cytokines to help regulate cellular growth as well as promote macrophage pro-inflammatory and antitumor activity.[53,70–72] (Fig. 1)

Mortality

The GDP in Recommendation 6 suggested empiric vitamin D supplementation in the general population aged 75 years and older because of the potential to lower risk of mortality. A meta-analysis examining the relationship between serum concentrations of 25(OH)D and all-cause mortality in 32 studies and pooled data revealed a significant inverse relationship. When comparing serum concentrations of 0-9 ng/mL to > 30 ng/mL there was a 90% reduced risk for mortality.[73] This remarkable inverse relationship with mortality and serum concentrations of 25(OH)D was confirmed[30] (Fig. 2 *K*). The Ludwigshafen Risk and Cardiovascular Health study of subjects referred for coronary angiography reported a substantial 75% reduction in all-cause mortality and 67% reduction in cardiovascular disease mortality in subjects with metabolic syndrome who had a circulating concentration of 25(OH)D of at least 30 ng/mL compared to those who were severely vitamin D deficient (<10 ng/mL).[74] Heath et al[75] evaluated vitamin D status and mortality in a systematic review of observational studies and concluded there was strong evidence that vitamin D status was inversely associated with all-cause mortality and may be beneficial for cancer and respiratory disease mortality. It is also worthwhile recognizing that there is a strong association with increased exposure to sunlight with decreased cardiovascular disease and noncancer mortality. Plausible explanations include that exposure to solar UVB radiation improves vitamin D status which has been demonstrated to be associated with lower cancer and CVD rates in observational studies.[25,29,42,43,63,65,69] It has also been hypothesized that exposure to solar UVA radiation which penetrates into the dermis causes the release of the vasodilator nitric oxide thereby improving cardiovascular health. Nitric oxide also regulates macrophage activation that is important for macrophage clearance of infectious agents and adaptive immunity responsiveness. Lack of nitric oxide causes a dysregulation of the NOD-, LRR- and pyrin domain-containing protein 3 inflammasone that has been associated with many chronic disorders including type 2 diabetes, Crohn's disease, and atherosclerosis.[76] (Fig. 1) An evaluation of data from the UK databank revealed that UV exposure from natural sunlight and/or from an artificial source, solarium, was inversely associated with all-cause mortality, cancer mortality, and CVD mortality. It was observed that solarium users had a serum 25(OH)D of 66.4 nmol/L (26.6 ng/mL) compared to nonuser 48.8 nmol/L (19.5 ng/mL).[77] Therefore, improvement in vitamin D status[78] along with sensible sun exposure that provides nitric oxide production in combination may be beneficial reducing risk for CVD and autoimmune disorders,[76-78] while improvement in vitamin D status alone appears to improve mortality from cancer.[65]

Concluding Remarks

Based on the GDP's guideline methodology and systematic literature review, the Endocrine Society no longer endorses specific 25(OH)D levels to define vitamin D sufficiency, insufficiency, and deficiency.[1] The GDP recognized the many significant limitations associated with their recommendations. Foremost is that many of the large RCTs. which they prioritized in their systematic review, had serum 25(OH)D concentrations at baseline that would be vitamin D sufficient/insufficient by the 2011 Guidelines[17] including the VITAL trial[11] of 31 ng/mL and the D2d trial of 28 ng/mL.[39] There are only 2 ways of achieving these baseline concentrations from diet/supplements and or sun exposure. A double-blind placebo-controlled study investigated circulating concentrations of 25(OH)D in 105 healthy subjects aged 18-79 years who were assigned either a placebo or 1000 IUs of vitamin D_2 or vitamin D_3 in a capsule or in orange juice daily for 11 weeks in mid-February in Boston. The mean baseline serum concentration of 25(OH)D in subjects who ingested 1000 IUs of vitamin D_2 or vitamin D_3 was 17.5 ng/mL and reached a mean peak concentration after 5 weeks of 28.1 ng/mL. The placebo group baseline was 19.8 ng/mL, and the final was 18.1 ng/mL.[79] Kroll et al[21] reported for male and female patients living in northern United States evaluating an average of 14,583 samples each week demonstrated the maximum seasonal increase at the end of the summer was 6.8 ng/mL. When 25(OH)D concentrations were at their lowest, more than 70% were less than 30 ng/mL and more than 40% were less than 20 ng/mL. (Fig. 2 *B*) Vitamin D deficiency [25(OH)D < 20 ng/mL] continues to be a worldwide health problem where in some countries including northern Europe, Middle East and Asia upwards of 90% were found to be vitamin D deficient.[78] (Fig. 3 *A*) A recent comprehensive evaluation of the vitamin D status of the American population from the NHANES (2001-2018) revealed the prevalence of serum concentrations of 25(OH)D < 10, 10-20, 20-30 and > 30 ng/mL was 2.6%, 22.0%, 40.9% and 34.5% in Americans aged > 1 year.(Fig. 3 *B*) People of color continue to be at much higher risk for vitamin D deficiency and insufficiency compared to non-Hispanic white adults. (Fig. 3 *C*) The authors reported that the prevalence of severe vitamin D deficiency [25(OH)D < 10 ng/mL] had not improved significantly and the moderate deficiency [25(OH)D = 10-20 ng/mL], insufficiency [25(OH)D 21-29 ng/mL] had a mild improvement due to several factors including i. increase health awareness of vitamin D health benefits ii. 25(OH)D assay testing, iii. increased supplement use: in 2003-2004 only 0.45% of adults (>20 years) took a vitamin D supplement of at least 1000 IUs daily compared to 16.12% in 2013-2014, and iv. more foods fortified with vitamin D.[79] Vitamin D deficiency and insufficiency remains a major health concern worldwide where it is estimated that approximately 40% of the population has a 25(OH)D < 20 ng/mL and 60% < 30 ng/mL.[78] (Fig. 3 *C*)

It has been estimated that for every 100 IUs of vitamin D obtained by the body, circulating concentrations of 25(OH)D increased by approximately ~0.7 ng/mL.[80,81] These observations are important when considering the next major limitation of the GDP's recommendations. They note unlike RCTs evaluating pharmaceutical agents where the intervention is compared to control participants who were not exposed to the intervention, it is not possible to have a true placebo for participants in vitamin D RCTs due to sun exposure, dietary, and supplemental sources and it is considered unethical not to provide vitamin D deficient subjects vitamin D, especially for long duration trials. Thus, many of the large RCTs permitted participants to have a supplement intake of 600-800 IUs daily. Since vitamin supplements contain 20-50% more active ingredients to maintain shelf life, the participants in the "placebo" group were most likely taking up to 1200 IUs daily. This would explain the baseline concentrations that were observed. In the Systematic Review[3] supporting the GDP's recommendations, it is stated that "10 clinical questions assessed the effect of vitamin D vs no vitamin D in the general population.". Clearly, this is an inaccurate statement based on their admitted limitation that the large studies that were the basis for their recommendations were assessing additional vitamin D versus adequate vitamin D for outcomes. Another limitation is that the trials that the panel considered were performed in overall healthy populations at average risk for the outcomes of interest; and therefore, limited their recommendations to generally healthy individuals. Based on the GDP's mandate, their recommendations were admittedly geared for public health and not for clinicians evaluating patients for medical conditions associated with calcium, phosphate and bone

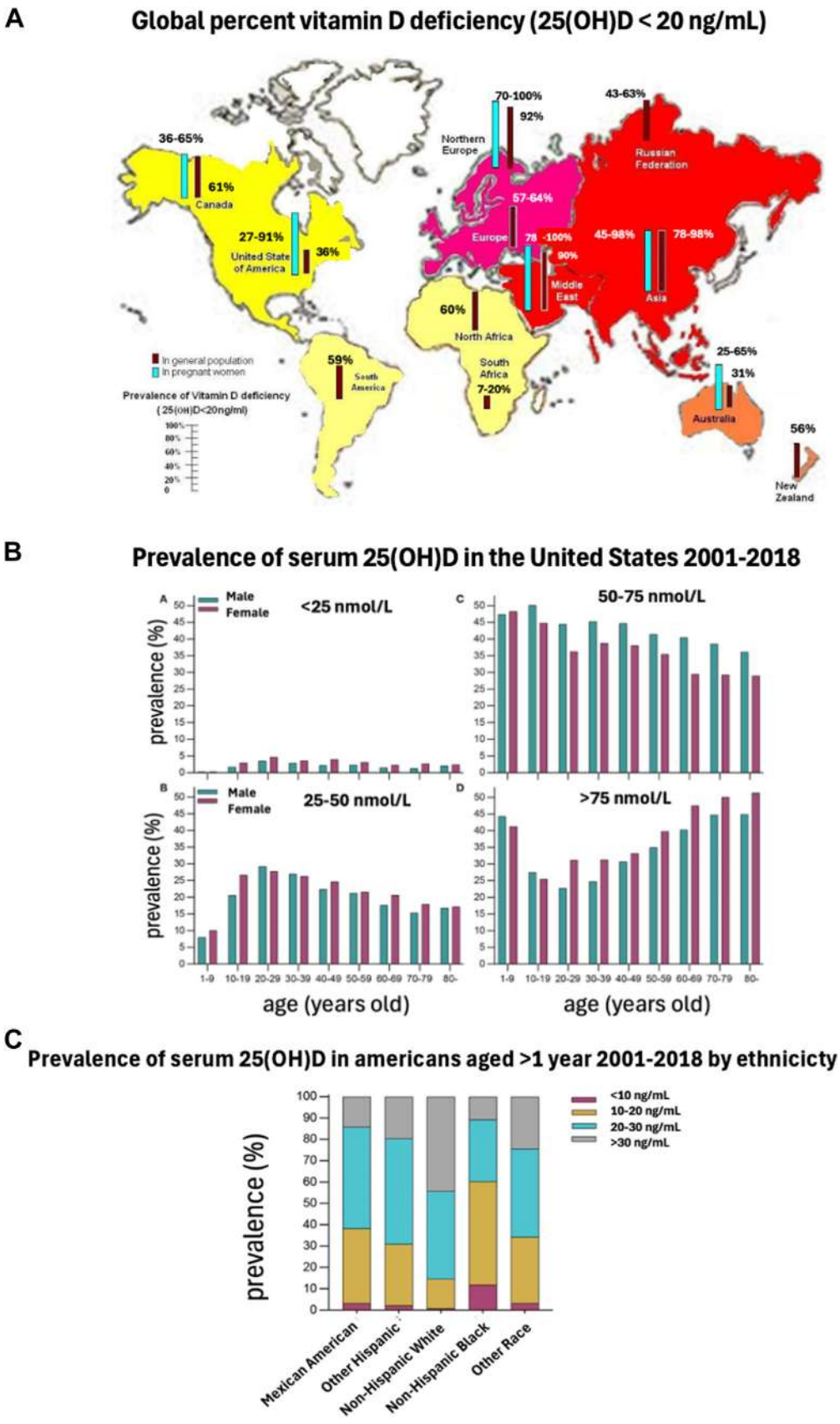

Fig. 3. Prevalence of vitamin D status as measured by circulating concentrations of 25-hydroxyvitamin D [25(OH)D]. *A*, Global vitamin D deficiency [25(OH)D <20 ng/mL] with permission Holick copyright 2013; *B*, Prevalence of serum concentrations of 25-hydroxyvitamin D [25(OH)D] in men and women in the United States 2001-2018 open access[79]; and *C*, Prevalence of serum concentrations of 25-hydroxyvitamin D [25(OH)D] in Americans aged >1 year 2001-2018 by ethnicicty.[79]

metabolism disorders. It would appear that the Endocrine Society in 2024[1] has become more interested in public health than in patient care that was the focus of the Endocrine Society in 2011.[17] The 2011 Guidelines[17] were written for health care professionals for how to i. evaluate patients at risk for vitamin D deficiency by measuring their circulating concentration of 25(OH)D and how to interpret the result, ii. treat vitamin D deficiency, and iii. how to prevent recurrence of vitamin D deficiency.

The GDP conducted a systematic literature review and prioritized 14 clinically relevant questions related to vitamin D.[3] They prioritize randomized placebo-controlled trials in general populations evaluating the effects of empiric vitamin D administration throughout the lifespan as well as selected conditions including pregnancy and prediabetes. They ignored association studies and did not provide any guidance for individuals with underlying conditions that substantially alter vitamin D physiology including patients with fat malabsorption syndromes, chronic kidney disease, hypocalcemia and hypercalcemia who could benefit from empiric vitamin D that was provided in the 2011 Guidelines.[17] The GDP acknowledged that empiric vitamin D, which may include daily intake of fortified foods, vitamin D formulations that contain vitamin D, and/or daily intake of a vitamin D supplement, is potentially beneficial for children and adolescents aged 1-18 years to prevent nutritional rickets and potentially lowering risk for respiratory tract infections, reducing risk of preeclampsia, infant mortality, preterm birth, small-for-gestational-age birth and neonatal birth, those with high risk for prediabetes to reduced progression to diabetes and for adults 75 years and older due to its potential lower risk of mortality. Therefore, it is reasonable based on the GDP's recommendation to provide empiric vitamin D supplementation recommendations for all children and adults. In the Guideline for recommending empiric vitamin D for children 1-18 years, the estimated weighted average of studies was 1200 IUs daily. Is the GDP and their Guidelines recommending that all children ages 1-18 take a vitamin D supplement since it is unrealistic that 1200 IUs daily can be obtained from the diet and fortified foods? The GDP ignored all association and other studies reporting that higher circulating concentrations of 25(OH)D of at least 30 ng/mL reduced risk of upper respiratory tract infections in young and middle-aged adults.[82,83] An analysis of 14,108 individuals over 16 years of age in the National Health and Nutrition Survey 2001-2006 reported after adjusting for season, demographic factors, and clinical data circulating concentrations of 25(OH)D < 30 ng/mL were associated with 58% higher odds of acute respiratory infection compared to concentrations >30 ng/mL.[82] Most importantly, they not only ignored the association with marked reduction in risks for COVID 19 infectivity, hospitalization, morbidity, and mortality in adults of all ages but also failed to recognize real placebo randomized controlled trials demonstrating that vitamin D supplementation markedly reduced risk of COVID 19 infection in health care workers exposed to COVID as well as reducing risk for morbidity and mortality.[26,49-52] Thus, it would have been much more appropriate if the GDP had not only included empiric vitamin D benefit for children but also for all adults since they are all at risk for acquiring this highly contagious disease and its attendant morbidity and mortality. Instead, the GDP recommended that all adults in the general population follow The DRI of 600-800 IUs vitamin D daily established by the IOM.[2] This amount of vitamin D is inadequate to maintain circulating concentrations of 25(OH)D of at least 30 ng/mL[51,52,80,81] to provide benefit against COVID 19 that has been demonstrated in placebo-controlled RCTs.

The CDC estimates that almost 50% of the U.S. population has either prediabetes (38%) or diabetes (11.6%). In Recommendation 10, the GDP recommends for adults with high risk for prediabetes that they would benefit by taking a weighted average of 3500 IUs vitamin D daily to reduce their risk of progressing to type 2 diabetes. This dose will achieve a circulating concentration of at least 30-40 ng/mL.[31](Fig. 2 *L*) With such a large percentage of the population (38%) having prediabetes, it would seem prudent to recommend that all adults maintain a circulating concentration of at least 30 ng/mL by taking a vitamin D supplement of 2000-4000 IUs daily for public health to reduce the incidence of type 2 diabetes. The logical alternative would have been to recommend vitamin D testing in patients with prediabetes and to recommend empiric vitamin D treatment for those who have a circulating concentration of 25(OH)D < 30 ng/mL.

According to the CDC, 41.9% of adults in the United States are obese. Obesity decreases the bioavailability of vitamin D produced in the skin from sun exposure and obtained orally due to its sequestration in body fat and redistribution in the body.[13,17,78] Ekwaru et al[31] analyzed 22,214 serum concentrations of 25(OH)D in adults encouraged to take a vitamin D supplement for health. They reported that to maintain the same circulating concentration of 25(OH)D, healthy obese adults require 2-3 times more vitamin D compared to normal weight adults as demonstrated in Figure 2 *M*. The GDP did not address this issue but did comment for Recommendation 14 that obese adults should not be screened for 25(OH)D. Obesity is associated with a 6-fold higher risk for type 2 diabetes compared to a healthy normal weight adult and thus for public health they should be screened for vitamin D deficiency and prediabetes and appropriately treated as recommended in the 2011 Guidelines.[17] The GDP recommended an estimated weighted average of 2500 IUs per day for improving pregnancy and birth outcomes. 25% of pregnant women in United States are obese. The GDP provided no guidance for whether they required higher vitamin D to experience the same benefit.

Finally, the GDP suggested that to improve mortality, adults 75 years and older should consider empiric vitamin D of approximately 900 IUs daily. This recommendation defies all logic. First, the major causes for mortality including cardiovascular disease, cancer, and respiratory illnesses are not initiated at age 75. The CDC on December 8, 2022, reported life expectancy for the U.S. population in 2021 was 76.4 years. Cardiovascular disease and cancer often are initiated decades earlier. It is more likely that early intervention with empiric vitamin D to maintain circulating concentrations of 25(OH)D of at least 30 ng/mL is necessary for reducing risk of these medical conditions that are ultimately responsible for mortality. The one exception is upper respiratory illnesses at all ages where vitamin D supplementation has been demonstrated to reduce risk, especially of COVID 19 infection in adults.[26] One of the studies to support Recommendation 7[3] was 12 weeks barely enough time to raise and maintain a new circulating concentration of 25(OH)D and certainly not enough time to have any impact on chronic medical conditions including cardiovascular disease and cancer associated with mortality. The GDP included the VITAL RCT[3] to justify the recommendation when there is little information on mortality for those 75 years and older. Neale et al[84] reported results from the D-Health Trial on adults 60 years and older (21% being 75 years and older) receiving 60,000 IUs vitamin D_3 monthly. Follow-up mean circulating concentration of 25(OH)D was 30.8 ng/mL and 46 ng/mL in the placebo and vitamin D treatment group, respectively. Not surprisingly, they concluded that monthly administration of vitamin D_3 did not reduce all-cause mortality in the placebo participants who were vitamin D sufficient. All the association and other studies have suggested that a circulating concentration of 25(OH)D at least 30 ng/mL was effective in reducing risk for mortality and very little additional benefit occurred thereafter.[30,73] (Fig. 2 *K*)

Thus, it would not be expected to see any significant difference in the placebo group with a circulating concentration of 25(OH)D of 31 ng/mL compared to the treatment group. All evidence suggests that it is the maintenance of a serum concentration of 25(OH)D of at least 30 ng/mL that reduces risk of mortality associated with cardiovascular disease, respiratory illnesses, and cancer.

Figure 2 displays a multitude of different association studies related to serum concentrations of 25(OH)D with various outcomes. From in utero until death, these association studies and other studies all point in the same direction. Vitamin D deficiency increases risk for poor pregnancy outcomes, early childhood dental caries, increased risk for autoimmune disorders, increased risk for upper respiratory tract infections including COVID 19, advancement of prediabetes to type 2 diabetes, cardiovascular disease, neurocognitive dysfunction, mortality and accelerating mortality from deadly cancers.[78] (Fig. 4) Most studies suggest that attaining a serum concentration of 25(OH)D of at least 30 ng/mL and up to 50 ng/mL provides the maximum benefit for various health outcomes. (Table 1)

The GDP should be recognized for bringing to the public's attention that empiric vitamin D supplementation has extraskeletal health benefits. The GDP recognized that one of the limitations, ie weaknesses of their recommendations based on the assessments of outcomes from RCTs that were not placebo-controlled trials but rather clinical trials that permitted the participant to ingest up to 800 IUs vitamin D daily. It was previously shown that healthy vitamin D deficient and insufficient adults ingesting 600 IUs daily for 6 months did not significantly change circulating concentrations of 25(OH)D (baseline 17.1 ± 5.9 and 24.3 ± 4.1 after 24 weeks) but still resulted in alterations in the expression of 162 genes.[6] Therefore, any RCT that has a "placebo" group that permits 600-800 IUs/D is receiving some vitamin D benefit thereby diluting the outcome measure related to the vitamin D treatment. The 2024 Guidelines[1] provide no recommendation for infants up to 1 year of age. This age group is extremely vulnerable to severe vitamin D deficiency especially if they are breast fed and do not receive vitamin D supplementation. The 2011 Guidelines[17] recommend all infants should receive at least 400 and up to 1000 IUs vitamin D daily; especially breast-fed infants. The 2024 Guidelines do not provide recommendations for amounts of vitamin D that can cause vitamin D intoxication. Vitamin D intoxication is extremely rare and due to intentional or inadvertent intake of extremely high doses of vitamin D in the range of more than 100,000 IUs daily for several months to several years. The 2011 Guidelines suggested that a circulating concentration of 25(OH)D > 150 ng/mL can result in evidence for vitamin D intoxication including early onset hypercalciuria and later hypercalcemia, hyperphosphatemia, soft tissue calcification including nephrocalcinosis that can lead to death.[13,17] The GDP recommendation that all adults in the general population should meet the DRI, which for adults up to 70 years is 600 IUs/day,

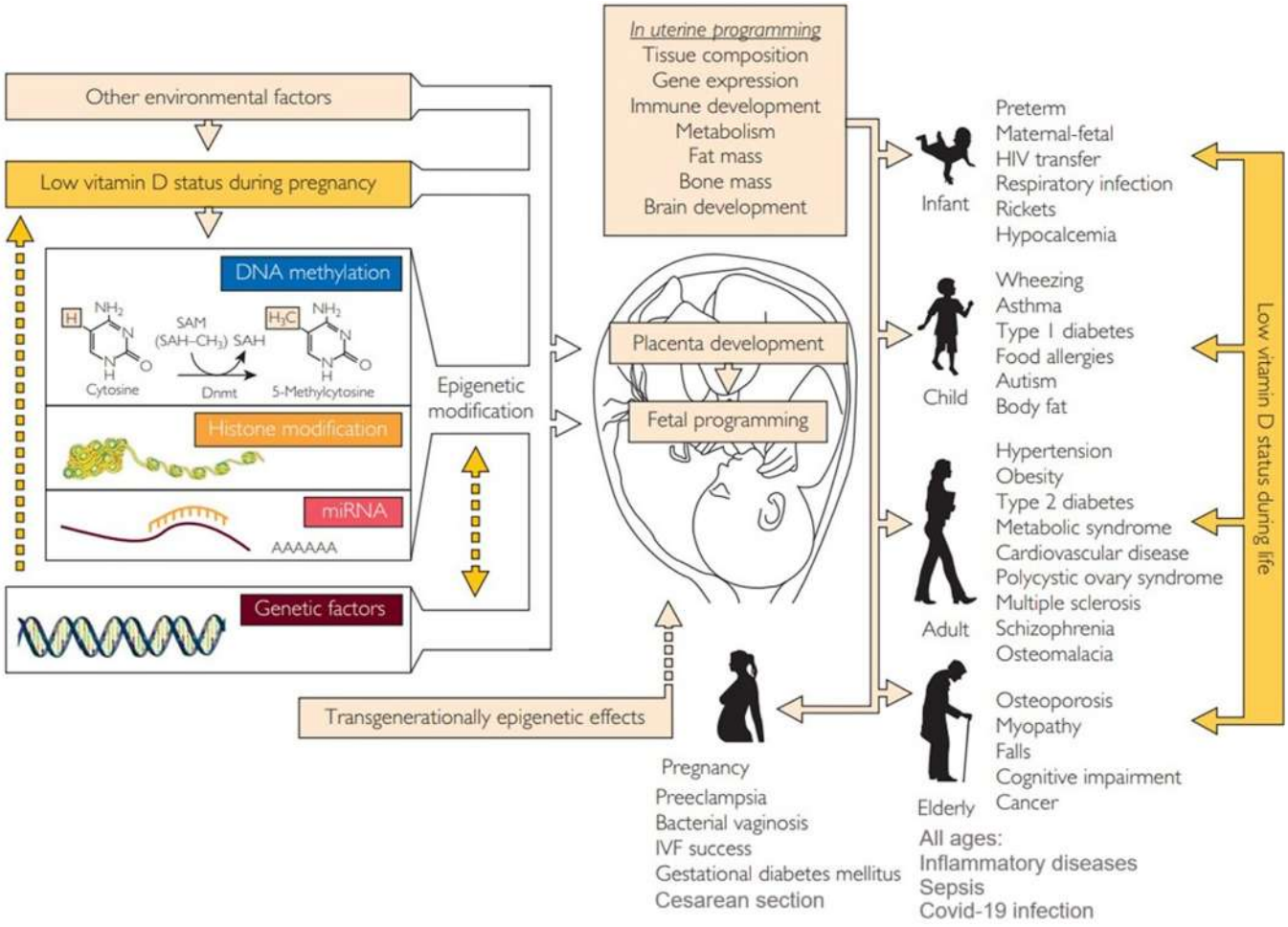

Fig. 4. Consequences of low (inadequate) vitamin D throughout life on clinical outcomes starting with placenta development, fetal programming, and epigenetic modification. *A* = adenosine; *CH3* = methyl group; *HIV* = human immunodeficiency virus; *IVF* = in vitro fertilization; *miRNA* = microRNA; *SAH* = S-adenosylhomocysteine; *SAM* = single carbon from adenosylmethionine. Copyright Holick 2013, reproduced with permission.

Table 1
Studies Relating Reduction in Clinical Outcomes and Serum Concentrations of 25-hydroxyvitamin D

Clinical outcome	Percent reduction	25-hydroxyvitamin D
1. Osteomalacia[22]	100%	≥ 30 ng/mL
2. Pre-eclampsia[23]	~ 60%	≥ 60 ng/mL
3. Premature births[24]	62%	≥ 40 ng/mL
4. Cesarean section births[34]	74%	≥ 40 ng/mL
5. Gestational diabetes[35]	50%	≥ 20 ng/mL
6. Infant dental caries[36]	75%	≥ 40 ng/mL
7. Prediabetes to diabetes[41]	76%	≥ 50 ng mL
8. Peripheral artery disease[25]	80%	≥ 29.2 ng/mL
9. Upper respiratory tract infections[82]	58%	≥ 30 ng/mL
10. COVID infectivity[26]	54%	≥ 34 ng/mL
11. COVID respiratory distress syndrome[50]	78%	≥ 30 ng/mL
12. COVID mortality[50]	66%	≥ 30 ng/mL
13. Multiple sclerosis[56]	62%	≥ 40 ng/mL
14. Autoimmune disorders[59]	39%	≥ 41.8 ng/mL
15. Colon cancer[64]	80%	≥ 33-41 ng/mL
16. Breast cancer [28]	50%	≥ 52 ng/mL
17. Digestive cancers relapse and death[69]	73%	≥ 40 ng/mL
18. All cause mortality[30]	>90%	≥ 33 ng/mL
19. Cardiovascular mortality[74]	67%	≥ 30 ng/mL
20. Cancer mortality[11]	25%	≥ 30 ng/mL

will not be effective in even maintaining a circulating concentration of 25(OH)D of at least 30 ng/mL[17,19,80,81] (Fig. 2 *L*) Vitamin D supplementation of at least 1500-2000 IUs/day as previously recommended by the 2011 Guidelines[17] for all adults including women of childbearing age will maintain circulating concentrations of 25(OH)D of at least 30 ng/mL. The National Institutes of Health estimates 5-8% of the US population has an autoimmune disorder and that 80% are women. The recent report from the VITAL trail[59] suggested that participants who ingested 2000 IUs daily reduced their risk of autoimmune disorders during the 5.3 years of evaluation including rheumatoid arthritis and psoriasis by 22%. When only the last 3 years of the intervention was considered, the group receiving 2000 IUs vitamin D_3 daily and who raised their serum concentration of 25(OH)D from 29.8 ng/mL to 41.8 ng/mL after 1 year had 39% fewer confirmed autoimmune diseases than the placebo group who started at essentially the same baseline and were permitted to take up to 800 IUs daily. The lack of any beneficial effect of being on the recommended DRI is supported by the observation that stopping the 2000 IUs vitamin D_3 supplementation for 2 years revealed the beneficial effect dissipated and that those observed for more than 2 years developed incident confirmed autoimmune disease compared to the placebo group.[60] If the pharmaceutical industry had developed a single drug capable of reducing cancer mortality by more than 25%, incidence of metastatic and fatal cancer by 38%, autoimmune disorders by 39% including type 1 diabetes by 88%, advancement of prediabetes to type 2 diabetes by 76%, peripheral vascular disease by 88%, lowering risk of respiratory tract infections by 58%, and COVID 19 infection, hospitalizations and mortality by as much as 74%, 22% and 45% respectively and accelerating COVID positive patients to COVID negativity by 66%, risk of preterm birth by 62%, and pre-eclampsia and need for a cesarean section by more than 50%, the drug would be heralded as a "miracle drug." (Table 1) With patent protection, this single drug sold worldwide would be the first trillion-dollar drug. The sunshine vitamin D provides all these health benefits especially when an adequate amount is taken to sustain circulating concentrations of 25(OH)D of at least 30 ng/mL, with the maximum benefit obtained with concentrations of 40-60 ng/mL. It should be appreciated that it was because of epidemiologic and association studies that prompted further investigations that even the GDP agrees has substantial health benefits especially related to pregnancy, diabetes, and infectious diseases. The GDP recognized that upward of 24% of children and adults in the United States and approximately 40% in Europe have a circulating concentration of 25(OH)D < 20 ng/mL. The IOM DRI recommendation of 600 IUs vitamin D daily will only sustain their circulating concentration of 25(OH)D, it does not improve it and therefore they will remain vitamin D deficient. Finally, it should be appreciated that it was association and epidemiologic observations that have been made over the past 100 years that provided the insights to evaluate vitamin D for nonskeletal health indications including reducing risk for poor pregnancy outcomes, diabetes, and

Table 2
Recommendations of the 2024 and 2011 Endocrine Society's Guidelines on Vitamin D

Age yrs	2024 Recommendation	2011 Recommendation	2011 UL Recommendation
0-1	No recommendation	400-1000 IUs	2000 IUs
1-18	Prevent nutritional rickets and potentially lower the risk of respiratory tract infections Dosage range 300-2000 IUs/day Estimated weighted average 1200 IUs/day	600-1000 IUs	4000 IUs
19-69	Dietary Recommended Intake 600 IUs/day	1500-2000 IUs	10000 IUs
70-74	Dietary Recommended Intake 800 IUs/day	1500-2000 IUs	10000 IUs
75	Recommend Vitamin D supplementation because of potential to lower risk of mortality Vitamin D dosage range 400-3333 IUs/day Estimated weighted average 900 IUs/day	1500-2000 IUs	10000 IUs
Special considerations			
Pregnancy	Recommend Vitamin D supplementation Given its potential to lower risk of pre-eclampsia Intrauterine mortality, preterm birth, small-for-gestational age birth, and neonatal mortality Dosage range 600-5000 IUs/day The estimated weighted average was approximately 2500 IUs/day	Ages 14-18 y 600-1000 IUs Ages 19 years and older 1500-2000 IUs	4000 IUs 10000 IUs
Adults with high risk diabetes	Vitamin D dosages range 842-7543 IUs/day The weighted average was approximately 3500 IUs/day	NA	NA

NA = Not applicable; *UL* = Upper limit.

infectious diseases in children. Since the GDP did not concern itself about the evaluation, treatment, and prevention of vitamin D deficiency, it is reasonable for health care professionals to utilize the 2011 Guidelines[17] for patient care for using the serum concentration of 25(OH)D to determine vitamin D status for patients at risk for vitamin D deficiency and treatment guidelines. Based on all the available information for the maximum health benefit of vitamin D supplementation, the 2011 Guideline recommendations for vitamin D supplementation will sustain a serum concentration of 25(OH)D of at least 30 ng/mL with the preferred range of 40-60 ng/mL. Table 2 summarizes recommendations of the GDP and 2011 Guidelines.

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References

1. Demay MB, Pittas AG, Bikle DD, et al. Vitamin D for the prevention of disease: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2024;109(8):1907–1947. https://doi.org/10.1210/clinem/dgae290
2. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the institute of medicine: what clinicians need to know. *J Clin Endocrinol Metab*. 2011;96(1):53–58. https://doi.org/10.1210/jc.2010-2704
3. Shah VP, Nayfeh T, Alsawaf Y, et al. A systematic review supporting the endocrine society clinical practice guidelines on vitamin D. *J Clin Endocrinol Metab*. 2024;109(8):1961–1974. https://doi.org/10.1210/clinem/dgae312
4. Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutrition Reviews*. 2014;72(1):48–54. https://doi.org/10.1111/nure.12090
5. Pilz S, Trummer C, Theiler-Schwetz V, et al. Critical appraisal of large Vitamin D randomized controlled trials. *Nutrients*. 2022;14(2):303. https://doi.org/10.3390/nu14020303
6. Shirvani A, Kalajian TA, Song A, Holick MF. Disassociation of Vitamin D's calcemic activity and non-calcemic genomic activity and individual responsiveness: a randomized controlled double-blind clinical trial. *Sci Rep*. 2019;9(1):17685. https://doi.org/10.1038/s41598-019-53864-1
7. Gospodarska E, Ghosh DR, Carlberg C. Intervention approaches in studying the response to Vitamin D_3 supplementation. *Nutrients*. 2023;15(15):3382. https://doi.org/10.3390/nu15153382
8. Zoltán I. "Ignaz semmelweis". In: *Encyclopedia Britannica*; 2024.. Accessed September 6, 2024. https://www.britannica.com/biography/Ignaz-Semmelweis
9. Mozołowski W. Jędrzej Sniadecki (1768–1838) on the cure of rickets. *Nature*. 1939;143:121.
10. Hess AF, Unger LJ. The Cure of infantile rickets by sunlight. *J Am Med Assoc*. 1921;77:39. https://doi.org/10.1001/jama.1921.02630270037013
11. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. *N Engl J Med*. 2019;380(1):33–44. https://doi.org/10.1056/NEJMoa1809944
12. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and incident fractures in midlife and older adults. *N Engl J Med*. 2022;387(4):299–309. https://doi.org/10.1056/NEJMoa2202106
13. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281. https://doi.org/10.1056/NEJMra070553
14. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006;116(8):2062–2072. https://doi.org/10.1172/JCI29449
15. Mathew J, Berger D, Tabatabaie V. Severe osteomalacia and fractures secondary to Vitamin D deficiency. *J Endocr Soc*. 2021;5(Suppl 1):A221. https://doi.org/10.1210/jendso/bvab048.449
16. Holick MF. *Vitamin D and bone health: what Vitamin D can and cannot do. Advances in Food and Nutrition Research*. Academic Press; 2024. ISSN 1043-4526.
17. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911–1930. https://doi.org/10.1210/jc.2011-0385
18. Chapuy MC, Schott AM, Garnero P, Hans D, Delmas PD, Meunier PJ. Healthy elderly French women living at home have secondary hyperparathyroidism and high bone turnover in winter. EPIDOS study group. *J Clin Endocrinol Metab*. 1996;81:1129–1133.
19. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *J Clin Endocrinol Metab*. 2005;90(6):3215–3224. https://doi.org/10.1210/jc.2004-2364
20. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338(12):777–783. https://doi.org/10.1056/NEJM199803193381201
21. Kroll MH, Bi C, Garber CC, et al. Temporal relationship between vitamin D status and parathyroid hormone in the United States. *PLoS One*. 2015;10(3):e0118108. https://doi.org/10.1371/journal.pone.0118108
22. Priemel M, von Domarus C, Klatte TO, et al. Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *J Bone Miner Res*. 2010;25(2):305–312. https://doi.org/10.1359/jbmr.090728
23. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *J Clin Endocrinol Metab*. 2007;92(9):3517–3522. https://doi.org/10.1210/jc.2007-0718
24. McDonnell SL, Baggerly KA, Baggerly CA, et al. Maternal 25(OH)D concentrations ≥40 ng/mL associated with 60% lower preterm birth risk among general obstetrical patients at an urban medical center. *PLoS One*. 2017;12(7):e0180483. https://doi.org/10.1371/journal.pone.0180483
25. Melamed ML, Muntner P, Michos ED, et al. Serum 25-hydroxyvitamin D levels and the prevalence of peripheral arterial disease: results from NHANES 2001 to 2004. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1179–1185. https://doi.org/10.1161/ATVBAHA.108.165886
26. Kaufman HW, Niles JK, Kroll MH, Bi C, Holick MF. SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. *PLoS One*. 2020;15(9):e0239252. https://doi.org/10.1371/journal.pone.0239252
27. Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. *Diabetologia*. 2008;51(8):1391–1398. https://doi.org/10.1007/s00125-008-1061-5
28. Garland CF, Gorham ED, Mohr SB, et al. Vitamin D and prevention of breast cancer: pooled analysis. *J Steroid Biochem Mol Biol*. 2007;103(3-5):708–711. https://doi.org/10.1016/j.jsbmb.2006.12.007
29. Garland FC, Garland CF, Gorham ED, Young JF. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev Med*. 1990;19(6):614–622. https://doi.org/10.1016/0091-7435(90)90058-r
30. Gaksch M, Jorde R, Grimnes G, et al. Vitamin D and mortality: individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. *PLoS One*. 2017;12(2):e0170791. https://doi.org/10.1371/journal.pone.0170791
31. Ekwaru JP, Zwicker JD, Holick MF, Giovannucci E, Veugelers PJ. The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. *PLoS One*. 2014;9(11):e111265. https://doi.org/10.1371/journal.pone.0111265
32. Tabesh M, Salehi-Abargouei A, Tabesh M, Esmaillzadeh A. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2013;98(8):3165–3173.
33. Mirzakhani H, Litonjua AA, McElrath TF, et al. Early pregnancy vitamin D status and risk of preeclampsia. *J Clin Invest*. 2016;126(12):4702–4715. https://doi.org/10.1172/JCI89031
34. Merewood A, Mehta SD, Chen TC, Bauchner H, Holick MF. Association between vitamin D deficiency and primary cesarean section. *J Clin Endocrinol Metab*. 2009;94(3):940–945. https://doi.org/10.1210/jc.2008-1217
35. Rostami M, Tehrani FR, Simbar M, et al. Effectiveness of prenatal Vitamin D deficiency screening and treatment program: a stratified randomized field trial. *J Clin Endocrinol Metab*. 2018;103(8):2936–2948. https://doi.org/10.1210/jc.2018-00109
36. Schroth RJ, Lavelle C, Tate R, Bruce S, Billings RJ, Moffatt ME. Prenatal vitamin D and dental caries in infants. *Pediatrics*. 2014;133(5):e1277–e1284. https://doi.org/10.1542/peds.2013-2215
37. Scragg R, Sowers M, Bell C, Third National Health and Nutrition Examination Survey. Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2004;27(12):2813–2818. https://doi.org/10.2337/diacare.27.12.2813
38. Wu J, Atkins A, Downes M, Wei Z. Vitamin D in diabetes: uncovering the sunshine hormone's role in glucose metabolism and beyond. *Nutrients*. 2023;15(8):1997. https://doi.org/10.3390/nu15081997
39. Pittas AG, Dawson-Hughes B, Sheehan P, et al. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med*. 2019;381(6):520–530. https://doi.org/10.1056/NEJMoa1900906

40. Dawson-Hughes B, Staten MA, Knowler WC, et al. Intratrial exposure to Vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the Vitamin D and type 2 diabetes (D2d) study. *Diabetes Care*. 2020;43(12):2916–2922. https://doi.org/10.2337/dc20-1765
41. Pittas AG, Kawahara T, Jorde R, et al. Vitamin D and risk for type 2 diabetes in people with prediabetes : a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann Intern Med*. 2023;176(3):355–363. https://doi.org/10.7326/M22-3018
42. Grübler MR, März W, Pilz S, et al. Vitamin-D concentrations, cardiovascular risk and events - a review of epidemiological evidence. *Rev Endocr Metab Disord*. 2017;18(2):259–272. https://doi.org/10.1007/s11154-017-9417-0
43. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. *Circulation*. 2008;117(4):503–511. https://doi.org/10.1161/CIRCULATIONAHA.107.706127
44. Dudenkov DV, Mara KC, Maxson JA, Thacher TD. Serum 25-hydroxyvitamin D values and risk of incident cardiovascular disease: a population-based retrospective cohort study. *J Steroid Biochem Mol Biol*. 2021;213:105953. https://doi.org/10.1016/j.jsbmb.2021.105953
45. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. *J Clin Endocrinol Metab*. 2010;95(10):4584–4591. https://doi.org/10.1210/jc.2010-0606
46. Raed A, Bhagatwala J, Zhu H, et al. Dose responses of vitamin D3 supplementation on arterial stiffness in overweight African Americans with vitamin D deficiency: a placebo controlled randomized trial. *PLoS One*. 2017;12(12):e0188424. https://doi.org/10.1371/journal.pone.0188424
47. Kumar V, Yadav AK, Lal A, et al. A randomized trial of Vitamin D supplementation on vascular function in CKD. *J Am Soc Nephrol*. 2017;28(10):3100–3108. https://doi.org/10.1681/ASN.2017010003
48. Acharya P, Dalia T, Ranka S, et al. The effects of Vitamin D supplementation and 25-hydroxyvitamin D levels on the risk of myocardial infarction and mortality. *J Endocr Soc*. 2021;5(10):bvab124. https://doi.org/10.1210/jendso/bvab124
49. Seal KH, Bertenthal D, Carey E, Grunfeld C, Bikle DD, Lu CM. Association of Vitamin D Status and COVID-19-related hospitalization and mortality. *J Gen Intern Med*. 2022;37:853–861. https://doi.org/10.1007/s11606-021-07170-0
50. Charoenngam N, Shirvani A, Reddy N, Vodopivec DM, Apovian CM, Holick MF. Association of Vitamin D status with hospital morbidity and mortality in adult hospitalized patients with COVID-19. *Endocr Pract*. 2021;27(4):271–278. https://doi.org/10.1016/j.eprac.2021.02.013
51. Villasis-Keever MA, López-Alarcón MG, Miranda-Novales G, et al. Efficacy and safety of Vitamin D supplementation to prevent COVID-19 in Frontline healthcare workers. A randomized clinical trial. *Arch Med Res*. 2022;53(4):423–430. https://doi.org/10.1016/j.arcmed.2022.04.003
52. Rastogi A, Bhansali A, Khare N, et al. Short term, high-dose vitamin D supplementation for COVID-19 disease: a randomised, placebo-controlled, study (SHADE study). *Postgrad Med J*. 2022;98(1156):87–90. https://doi.org/10.1136/postgradmedj-2020-139065
53. Charoenngam N, Holick MF. Immunologic effects of Vitamin D on human health and disease. *Nutrients*. 2020;12(7):2097. https://doi.org/10.3390/nu12072097
54. Sintzel MB, Rametta M, Reder AT. Vitamin D and multiple sclerosis: A comprehensive review. *Neurol Ther*. 2018;7(1):59–85. https://doi.org/10.1007/s40120-017-0086-4
55. Munger KL, Zhang SM, O'Reilly E, et al. Vitamin D intake and incidence of multiple sclerosis. *Neurology*. 2004;62(1):60–65. https://doi.org/10.1212/01.wnl.0000101723.79681.38
56. Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyvitamin D levels and risk of multiple sclerosis. *JAMA*. 2006;296(23):2832–2838. https://doi.org/10.1001/jama.296.23.2832
57. Munger KL, Åivo J, Hongell K, Soilu-Hänninen M, Surcel HM, Ascherio A. Vitamin D status during pregnancy and risk of multiple sclerosis in offspring of women in the finnish maternity cohort. *JAMA Neurol*. 2016;73(5):515–519. https://doi.org/10.1001/jamaneurol.2015.4800
58. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. *The Lancet*. 2001;358(9292):1500–1503.
59. Hahn J, Cook NR, Alexander EK, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. *BMJ*. 2022;376:e066452. https://doi.org/10.1136/bmj-2021-066452
60. Costenbader KH, Cook NR, Lee IM, et al. Vitamin D and marine n-3 fatty acids for autoimmune disease prevention: outcomes two years after completion of a double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2024;76(6):973–983. https://doi.org/10.1002/art.42811
61. Peller S, Stephenson CS. Skin irritation and cancer in the United States Navy. *Am J Med Sci*. 1937;194:326–333.
62. Apperly FL. The relation of solar radiation to cancer mortality in North American. *Cancer Res*. 1941;1:191–195.
63. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*. 1980;9(3):227–231. https://doi.org/10.1093/ije/9.3.227
64. Garland C, Garland F, Shaw E, Comstock G, Helsing K, Gorham E. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *The Lancet*. 1989;334(8673):1176–1178.
65. Grant WB. An estimate of premature cancer mortality in the U.S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer*. 2002;94(6):1867–1875. https://doi.org/10.1002/cncr.10427
66. Keum N, Lee DH, Greenwood DC, Manson JE, Giovannucci E. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. *Ann Oncol*. 2019;30(5):733–743. https://doi.org/10.1093/annonc/mdz059
67. Chandler PD, Chen WY, Ajala ON, et al. VITAL research group. Effect of Vitamin D3 supplements on development of advanced cancer: a secondary analysis of the vital randomized clinical trial. *JAMA Netw Open*. 2020;3(11):e2025850.
68. Urashima M, Ohdaira H, Akutsu T, et al. Effect of Vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial. *JAMA*. 2019;321(14):1361–1369. https://doi.org/10.1001/jama.2019.2210
69. Kanno K, Akutsu T, Ohdaira H, Suzuki Y, Urashima M. Effect of Vitamin D supplements on relapse or death in a p53-immunoreactive subgroup with digestive tract cancer: post hoc analysis of the AMATERASU randomized clinical trial. *JAMA Netw Open*. 2023;6(8):e2328886. https://doi.org/10.1001/jamanetworkopen.2023.28886
70. Holick MF. The one-hundred-year anniversary of the discovery of the sunshine Vitamin D_3: historical, personal experience and evidence-based perspectives. *Nutrients*. 2023;15(3):593. https://doi.org/10.3390/nu15030593
71. Carlberg C, Munoz A. An update on vitamin D signaling and cancer. *Seminars in Cancer Biology*. 2022;79:217–230. https://doi.org/10.1016/j.semcancer.2020.05.018
72. Negri M, Gentile A, de Angelis C, et al. Vitamin D-induced molecular mechanisms to potentiate cancer therapy and to reverse drug-resistance in cancer cells. *Nutrients*. 2020;12(6):1798. https://doi.org/10.3390/nu12061798
73. Garland CF, Kim JJ, Mohr SB, et al. Meta-analysis of all-cause mortality according to serum 25-hydroxyvitamin D. *Am J Public Health*. 2014;104(8):e43–e50. https://doi.org/10.2105/AJPH.2014.302034
74. Thomas GN, ó Hartaigh B, Bosch JA, et al. Vitamin D levels predict all-cause and cardiovascular disease mortality in subjects with the metabolic syndrome: the Ludwigshafen risk and cardiovascular health (LURIC) study. *Diabetes Care*. 2012;35(5):1158–1164. https://doi.org/10.2337/dc11-1714
75. Heath AK, Kim IY, Hodge AM, English DR, Muller DC. Vitamin D status and mortality: a systematic review of observational studies. *Int J Environ Res Public Health*. 2019;16(3):383. https://doi.org/10.3390/ijerph16030383
76. Stevenson AC, Clemens T, Pairo-Castineira E, Webb DJ, Weller RB, Dibben C. Higher ultraviolet light exposure is associated with lower mortality: An analysis of data from the UK biobank cohort study. *Health Place*. 2024;89:103328. https://doi.org/10.1016/j.healthplace.2024.103328
77. Sutherland JP, Zhou A, Hyppönen E. Vitamin D deficiency increases mortality risk in the UK biobank: a nonlinear mendelian randomization study. *Ann Intern Med*. 2022;175(11):1552–1559. https://doi.org/10.7326/M21-3324
78. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc*. 2013;88(7):720–755. https://doi.org/10.1016/j.mayocp.2013.05.011
79. Cui A, Xiao P, Ma Y, et al. Prevalence, trend, and predictor analyses of vitamin D deficiency in the US population, 2001-2018. *Front Nutr*. 2022;9:965376. https://doi.org/10.3389/fnut.2022.965376
80. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. *J Clin Endocrinol Metab*. 2008;93(3):677–681. https://doi.org/10.1210/jc.2007-2308
81. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr*. 2003;77(1):204–210. https://doi.org/10.1093/ajcn/77.1.204
82. Monlezun DJ, Bittner EA, Christopher KB, Camargo CA, Quraishi SA. Vitamin D status and acute respiratory infection: cross sectional results from the United States National Health and Nutrition Examination Survey, 2001-2006. *Nutrients*. 2015;7(3):1933–1944. https://doi.org/10.3390/nu7031933
83. Ginde AA, Mansbach JM, Camargo Jr CA. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2009;169(4):384–390. https://doi.org/10.1001/archinternmed.2008.560
84. Neale RE, Baxter C, Romero BD, et al. The D-Health Trial: a randomised controlled trial of the effect of vitamin D on mortality. *Lancet Diabetes Endocrinol*. 2022;10(2):120–128. https://doi.org/10.1016/S2213-8587(21)00345-4