Regence

Medical Policy Manual Laboratory, Policy No. 52

Vitamin D Testing

Effective: February 1, 2026

Next Review: October 2026
Last Review: December 2025

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Vitamin D is a fat-soluble vitamin that plays an essential role in mineral metabolism (e.g. calcium absorption) and is needed for normal bone growth and remodeling. In addition, the vitamin has several other roles, including but not limited to modulation of neuromuscular and immune functions.

MEDICAL POLICY CRITERIA

I. 25-hydroxyvitamin D [25(OH)D], calcidiol, serum testing may be considered **medically necessary** in individuals with a clinically documented underlying disease or condition which is specifically associated with vitamin D deficiency or decreased bone density as listed in Appendix I.

II. 25(OH)D serum testing is considered **not medically necessary** unless there is clinical documentation of an underlying disease or condition specifically associated with vitamin D deficiency or decreased bone density as listed in Appendix I.

III. 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] calcitriol, serum testing may be **medically necessary** in the evaluation or treatment of conditions that may be associated with defects in vitamin D metabolism as listed in Appendix II.

IV. 1,25(OH)$_2$D serum testing is considered **not medically necessary** unless there is clinical documentation of a condition specifically associated with defects in vitamin D metabolism as listed in Appendix II.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

LIST OF INFORMATION NEEDED FOR REVIEW

SUBMISSION OF DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes. Including documentation of serum testing and applicable treatment history of underlying disease/condition associated with vitamin D deficiency, decreased bone density or vitamin D metabolism defect.
- Diagnosis

CROSS REFERENCES

1. Folate Testing, Laboratory, Policy No. 79
2. Biomarkers for Cardiovascular Disease, Laboratory, Policy No. 80

BACKGROUND

Vitamin D, also known as calciferol, is a fat-soluble vitamin that has a variety of physiologic effects, most prominently in calcium homeostasis and bone metabolism. In addition to the role it plays in bone metabolism, other physiologic effects include inhibition of smooth muscle proliferation, regulation of the renin-angiotensin system, decrease in coagulation, and decrease in inflammatory markers.

Vitamin D intake (food and supplements) can be expressed in either International Units (IU) or micrograms (µg) (1 µg = 40 IU vitamin D).

Vitamin D is available from a limited number of dietary sources (fish liver oils, fatty fish, egg yolks, and fortified foods), supplementation, and from skin synthesis upon exposure to ultraviolet radiation from the sun.

There are two forms of activated vitamin D for which testing is performed:

- 25-hydroxyvitamin D [25(OH)D], calcidiol

  This is the most abundant circulating form of vitamin D and is the most common measure of serum levels.

- 1,25-dihydroxyvitamin D [1,25(OH)$_2$D], calcitriol

  Although the most metabolically active form, circulating 1,25(OH)$_2$D is generally not considered to be a reliable measurement of vitamin D as it has a very short half-life. Production in the kidney is closely regulated by a number of different factors, and a

significant decrease is observed only when deficiency is severe. However, there may be a role for 1,25-dihydroxyvitamin D serum testing in the evaluation and treatment of a limited number of medical indications (see Appendix II).[1-4] For these conditions, *1,25(OH)$_2$D* serum testing is not a measure of vitamin D deficiency related to inadequate sunlight and/or nutritional exposure. Rather, the test is a measure of abnormal vitamin D metabolism and may be an indicator of disease.

Vitamin D testing to determine serum levels may be performed for two purposes:

- To assess serum levels in patients with signs and/or symptoms of toxicity or deficiency or with conditions strongly associated with vitamin D deficiency (see Appendices I & II); or
- To screen for potential deficiencies in:
    - Healthy individuals without signs or symptoms of an illness/disease (e.g., vitamin D screening as a part of routine health exams); or
    - Individuals with general symptoms which are not specific to or suggestive of vitamin D deficiency.

EVIDENCE SUMMARY

It is widely recognized that there are some disorders which are thought to be *caused* or *exacerbated* by vitamin D deficiency. In general, these disorders are related to bone health, such as rickets, osteomalacia, and osteoporosis. In addition, there are certain medical conditions which may *result* in vitamin D deficiency, such as chronic kidney disease, sarcoidosis and malabsorption disorders. There is strong medical consensus that vitamin D testing and treatment is appropriate when these specific conditions (see Appendices I and II) directly cause or result in vitamin deficiency. Specifically, for these patients, treatment of a detected vitamin D imbalance is thought to directly improve health outcomes. With the exception of testing for bone health disorders, the evidence regarding the causal relationship between vitamin D deficiency and these specific conditions is limited; however, assessment of serum levels in patients with these conditions is widely accepted and has become the standard of care.

Vitamin D testing has also been proposed as part of routine wellness check-ups in asymptomatic patients and in patients who present with a variety of conditions or symptoms not specifically associated with vitamin D deficiency. For many of these indications, evidence has accumulated which supports an association between vitamin D deficiency and the symptom or condition. However, there is limited evidence to establish a causal relationship or demonstrate that treatment based on vitamin D test results leads to an improvement in health outcomes associated with these indications.

Current guidelines for establishing causality require direct evidence which demonstrates that the effect of treating vitamin D deficiency is greater than the combined influence of all confounding factors for the given condition.[5] This direct evidence could come from well-designed, randomized controlled trials. Evidence from non-randomized trials may also be considered when vitamin D supplementation results in an improvement of symptoms which is so sizable that the health improvement rules out the combined effect of all other possible causes of the condition. Currently, evidence of this magnitude is limited with respect to vitamin

D treatment in patients with or without a known condition. Therefore, in order to isolate the independent contribution of vitamin D testing on health outcomes, studies which control for confounding factors are essential. Large, well-designed, randomized controlled trials (RCTs) with adequate follow-up are needed.

METHODS OF EVIDENCE ASSESSMENT

Validation of the clinical use of any diagnostic test requires the demonstration of three key components:

Analytic validity, including reproducibility and precision. For comparison among studies, a common standardized protocol for the new diagnostic technology is established.

Clinical validity (i.e., sensitivity, specificity, and positive and negative predictive value) which describes the ability of a test to accurately predict clinical outcomes in appropriate populations of patients. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive). The specificity is the ability to detect the absence of a disease or outcome when the disease is not present (true negative).

In general, systematic reviews and evidence reports regarding the technical feasibility and diagnostic performance of vitamin D testing indicate there is uncertainty associated with this measurement.[6-9] The appropriate testing method[6, 8] and cut-off values for optimal serum levels of vitamin D have not been defined.[8-10]

After reviewing evidence from more than a thousand studies the Institutes of Medicine (IOM) 2010 report committee concluded that, “the measurements, or cut-points, of sufficiency and deficiency used by laboratories to report results have not been set based on rigorous scientific studies, and no central authority has determined which cut-points to use. A single individual might be deemed deficient or sufficient, depending on the laboratory where the blood is tested.”[7] Without established cut-off values and reference standards, vitamin D tests may produce false results that in turn may mislead treatment decisions.

Despite uncertain evidence, the IOM report recommended an adequate intake (AI) of 600 IU for males and females between 1 and 70 years of age, and 800 IU for adults 71 years and older (recommended adequate intake is defined as average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people).[7]

Clinical utility is a key aspect of evaluating clinical test performance, and it demonstrates how the results of a study can be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes. The clinical utility of both positive and negative tests must be established.

The focus of the following literature review is on evidence related to the clinical utility of vitamin D testing for indications not otherwise listed in Appendices I and II. In order to establish clinical utility, evidence from randomized controlled trials is required to demonstrate the following:

1. How test results are used to guide treatment decisions that would not otherwise be made in the absence of testing, and
2. Whether those decisions result in improved primary health outcomes associated with the disease or condition being treated.

The focus of the following evidence summary is on well-designed RCTs (including large patient

groups, and long-term follow-up), and systematic reviews of RCTs. A large number of RCTs have evaluated the impact of vitamin D supplementation on outcomes. Because of the large literature base, this review of evidence will focus on the largest and most recent systematic reviews and meta-analyses of RCTs.

ALZHEIMER'S DISEASE

SYSTEMATIC REVIEWS

Several systematic reviews reported an association between Alzheimer's disease and vitamin D deficiency when compared to healthy controls; however, the effect of vitamin D supplementation on patients with Alzheimer's disease was not assessed.[11-16] Therefore, the clinical utility of testing and treating for vitamin D deficiency has not been established.

Additional reviews of published studies regarding vitamin D supplementation as a treatment for Alzheimer's disease have been published; however, these reviews are based upon non-randomized prospective studies, which are not considered reliable for establishing the clinical utility of testing.

RANDOMIZED CONTROLLED TRIALS

Stein (2011) evaluated vitamin D and nasal insulin treatment on memory and disability in 32 patients with mild-moderate Alzheimer's disease (AD).[17] All patients took low-doses of vitamin D (1000 IU/day) throughout the study and were then randomized to additional high-doses of vitamin D for eight weeks. After eight weeks, patients were then randomized again to nasal insulin (60 IU qid) or placebo for 48 hours. Primary outcomes were measured with Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), Disability Assessment in Dementia (after high-dose D) and ADAS-cog and Wechsler Memory Scale-Revised Logical memory (WMS-R LM) for immediate and delayed recall (after nasal insulin). There were no reported differences in cognition or disability after high-dose vitamin D compared to the control group. In addition, this study is limited by small sample size, short-term follow-up and the addition of a confounding variable of the second medication (nasal insulin).

ANOREXIA NERVOSA

Anorexia nervosa is associated with many nutritional deficiencies, including vitamin D deficiency, and osteopenia and osteoporosis are common in patients with this disorder. A meta-analysis of cross-sectional studies reported that patients with anorexia nervosa have reduced serum 25(OH)D compared with health controls and that supplementation can increase these levels,[18] however no RCTs or systematic reviews evaluating vitamin D supplementation on health outcomes in patients with anorexia nervosa were identified.

ASTHMA AND WHEEZING

SYSTEMATIC REVIEWS

Several systematic reviews of vitamin D supplementation for the prevention of asthma exacerbation have been published. Three recent reviews are summarized in Table 1.

The Liu (2022),[19] Jolliffe (2017),[20] and Williamson (2023)[21] reviews concluded that the RCTs were generally at low risk of bias. The RCTs included children and adults, as well as variable doses of vitamin D, routes and lengths of administration, and variable levels of asthma

severity. The RCTs also included patients with variable baseline 25(OH)D levels and patients were not generally selected by baseline 25(OH)D. The Jolliffe (2017) review found that vitamin D supplementation reduced the rate (or proportion) of asthma exacerbations requiring treatment with systemic corticosteroids, while Liu (2022) found vitamin D supplementation to reduce overall asthma exacerbations. Liu (2022 found no benefit to vitamin D supplementation on ACT scores, FEV1, or fractional exhaled nitric oxide (FENO). The Jolliffe review used individual participant data and was therefore able to test for patient-level subgroup effects. For the outcome of “rate of asthma exacerbations treated with systemic corticosteroids,” the protective effect of vitamin D was larger in patients with a baseline 25(OH)D levels of less than 25 nmol/L (rate ratio 0.33, 95% confidence interval [CI] 0.11 to 0.98) compared with patients who had higher a baseline 25(OH)D levels (rate ratio 0.77, 95% CI 0.58 to 1.03). However, the subgroup by treatment group interaction was not statistically significant (p=0.25). The updated Cochrane review published by Williamson (2023)[21] included 20 RCTs and found no effect on the proportion of patients with asthma exacerbations, the rate of exacerbations, or any secondary efficacy outcome, including the incidence of asthma exacerbations leading to an emergency department visit and/or hospital admission, ACT scores, and FEV1.

Table 1. Vitamin D and Asthma Systematic Review Characteristics

Study (Year)	Dates	Trials	Participants	N	Design	Duration
Williamson (2023)[21]	Up to Sept 2022	20	People with asthma, all ages	2,225	Randomized controlled trials	3 to 40 months
Liu (2022)[22]	The decade prior to publication	10	Asthma patients who received any form or dose of vitamin D	1,349	Randomized controlled trials	9 weeks to 12 months
Jolliffe (2017);[20] PROSPERO CRD42014013953	Up to Oct 2016	8	People with asthma, all ages, and baseline 25(OH)D levels included	1,078	Randomized, double-blind, placebo-controlled	15 weeks to 12 months

RCT: randomized controlled trial; 25(OH)D: 25-hydroxyvitamin D.

RANDOMIZED CONTROLLED TRIALS

Additional RCTs of vitamin D supplementation and asthma not already included in the above referenced review are summarized here.

An RCT of prenatal supplementation in 881 pregnant women at high risk of having children with asthma was published in 2016.[23] Women between gestational ages of 10 and 18 weeks were randomized to daily vitamin D 4000 IU plus a multivitamin containing vitamin D 400 IU (4400 IU group) or daily placebo vitamin D plus a multivitamin containing vitamin D 400 IU (400 IU group). Coprimary outcomes were (1) parental report of physician-diagnosed asthma or recurrent wheezing through three years of age and (2) third trimester maternal 25OH(D) levels. Analysis of infant outcomes included 806 infants, 218 of whom developed asthma by

age three. The proportion of infants with asthma or recurrent wheeze was 24% in the 4400 IU group versus 30% in the 400 IU group (difference -6%, 95% CI -30% to 18%). There were no differences in the proportion of infants experiencing eczema or lower respiratory tract infections. After six years of follow-up, no benefit was found for prenatal vitamin D supplementation on asthma or recurrent wheeze in the children.[24]

CANCER

SYSTEMATIC REVIEWS

Keum (2019) published a meta-analysis of RCTs evaluating vitamin D supplementation on cancer incidence and mortality.[25] Ten RCTs (6,537 cases) were included in the cancer incidence analysis, six of which provided daily vitamin D3 (400-2000 IU/day) and four of which provided D3 in a large, nondaily bolus (20,000 IU/week to 500,000 IU/year). This analysis found no difference between supplementation and control groups for cancer incidence. Five RCTs were included in the analysis of cancer mortality, which found a reduced risk of mortality in the supplementation group (relative risk [RR] 0.85, 95% CI 0.75 to 0.97, p=0.02, I^2=0%), though none of the individual studies showed a statistically significant difference. This difference was present when the analysis was limited to daily supplementation studies, but not bolus supplementation, and was present even when circulating 25(OH)D levels were at or below 100 nmol/L.

In 2014, a Cochrane systematic review and meta-analysis assessed the benefits and harms of vitamin D supplementation on prevention of cancer in adults.[26] Reviewers included 18 RCTs (50,623 participants) that compared vitamin D at any dose, duration, and route of administration to placebo or no intervention in healthy adults or diagnosed with a specific disease. Cancer occurred in 1,927 (7.6%) of 25,275 participants assigned to receive vitamin D versus 1,943 (7.7%) of 25,348 participants assigned to receive control interventions (RR 1.00, 95% CI 0.94 to 1.06) based on GRADE moderate quality evidence. There was no substantial difference in the effect of vitamin D on cancer in subgroup analyses of trials only including participants with vitamin D levels less than 20 ng/mL at enrollment compared to trials including participants with vitamin D levels of 20 ng/mL or greater at enrollment. Vitamin D_3 combined with calcium was associated with increased nephrolithiasis (RR 1.17, 95% CI 1.03 to 1.34).

A 2014 AHRQ report summarized the evidence on vitamin D supplementation and cancer outcomes.[27] Based on a limited number of RCTs, the following conclusions were made:

- One RCT reported no effect of vitamin D on overall cancer mortality in healthy postmenopausal women.
- One RCT reported no effect of vitamin D on overall cancer mortality for elderly men or women.

The evidence on the association between vitamin D levels and cancer was reviewed by the Institute of Medicine in 2011, with the following conclusions:[7]

- There are a small number of studies that address this question and they show a lack of consistency in associations between vitamin D intake, or levels, and all cancer mortality.
- Most available RCTs do not have cancer as a prespecified primary outcome, thus the validity of the data is less than optimal.
- Overall, the evidence is insufficient to form conclusions about the association of vitamin D with cancer.

RANDOMIZED CONTROLLED TRIALS

Additional RCTs evaluating vitamin D supplementation and serum testing in the treatment and prevention of cancer that are not already included in the reviews referenced above are summarized here.

Chatterjee (2021) published an ancillary study to the Vitamin D and type 2 diabetes (D2d) study, which focused on cancer outcomes in patients with prediabetes and overweight/obesity who were randomized to receive vitamin D3 (4000 IU daily) or placebo.[28] Cancer or precancer events were identified during quarterly study visit questionnaires, for a median follow-up time of 2.9 years. Among the 2,385 participants, 89 developed cancer and 239 had colorectal adenomatous polyps identified during the study. Vitamin D supplementation was not significantly associated with either outcome.

Ammann (2017) reported results of a secondary analysis from the Women's Health Initiative (WHI) Calcium/Vitamin D (CaD) trial.[29] Participants were offered to participate in the CaD at their first follow-up visit for the large WHI trials between 1995 and 2000. A total of 36,282 women were stratified by treatment location and age and randomized to calcium (1000 mg of elemental calcium carbonate) and vitamin D (400 IU of D3) or placebo in a 1:1 allocation. Daily non-study calcium and vitamin D supplements were also allowed. Data not included in analysis did not differ between arms (data were excluded for missingness or diagnosis of a hematopoietic malignancy prior to the start of the CaD trial), nor did length of follow-up. Total participant data included in final analysis included 17,411 in active treatment, and 17,352 in the control arm (total n=34,763). Primary endpoints were 1) incident hematologic malignancy (all types), and 2) hematologic cancer-specific mortality. Median follow-up was seven years; median age (range) was 63 (58 to 69) for both arms. Overall risk of hematologic malignancy was found to be statistically lower in the intervention arm compared to the control arm (HR 0.80, 95% CI 0.65 to 0.99, p=0.04). However, no significant association was found between CaD supplementation and hematologic-cancer specific mortality (HR 0.77, 95% CI 0.53 to 1.11, p=0.16). Following the results of this large, well designed RCT, authors concluded additional research regarding the association between vitamin D supplementation and hematologic malignancies is warranted.

CARDIOVASCULAR DISEASE

SYSTEMATIC REVIEWS

A systematic review by Su (2021) assessed 36 studies that included cohort studies, RCTs, and case-control analyses for the association between serum levels of vitamin D and risk of stroke.[30] Lower levels of serum vitamin D were associated with an elevated risk of stroke in both Asian and White populations, however, vitamin D supplementation did not show benefit in decreasing the risk of stroke. In a meta-analysis limited to RCTs, Fu (2022) had similar findings; vitamin D did not reduce stroke risk compared with placebo (relative risk 1.02, 95% CI 0.93 to 1.13, p=0.65).[31]

A systematic review and regression meta-analysis by Nudy (2020) analyzed the effect of vitamin D supplementation on the risk of coronary heart disease (CHD) and stroke, using data from 22 RCTs (total n=83,200).[32] In the 21 trials (n=83,093) that reported CHD events, the weighted mean age of participants was 65.7 years, and the mean follow-up was 2.6 years. Vitamin D supplementation was not associated with any difference in cardiovascular events, including nonfatal myocardial infarction, cardiac death, stroke, or CHD events.

Elamin (2011) published a systematic review and meta-analysis evaluating cardiovascular outcomes.[33] It included 51 trials that used various forms of vitamin D with or without calcium. There was minimal heterogeneity among the studies. Combined analysis showed no significant impact on cardiovascular death (RR 0.96, 95% CI 0.93 to 1.0), myocardial infarction (RR 1.02, 95% CI 0.93 to 1.13), or stroke (RR 1.05, 95% CI 0.88 to 1.25). No significant effects were found on the physiologic outcomes of lipids, glucose, or blood pressure.

A systematic review by Pittas (2010) assessed five RCTs evaluating the impact of vitamin D supplementation on incident cardiovascular disease.[34] None of the five trials reported a significant reduction in cardiovascular outcomes in the vitamin D group. Combined analysis of these trials found a RR for cardiovascular outcomes of 1.08 (95% CI 0.99 to 1.19) in the vitamin D group.

An AHRQ report by Chung (2009) concluded that:[35]

- The evidence on the impact of vitamin D on cardiovascular outcomes is inconsistent, and conclusions are difficult to make because of the marked heterogeneity of the evidence.
- The RCTs that have evaluated the impact of vitamin D on cardiovascular outcomes use cardiovascular events as a secondary outcome, not as a prespecified primary outcome.
- These analyses have been hampered by low numbers of cardiovascular events and imperfect methods for the ascertainment of cardiovascular events.

Wang (2010) published a systematic review on vitamin D and calcium supplementation for the prevention cardiovascular events.[36] Eight RCTs of vitamin D supplementation in the general population evaluated cardiovascular outcomes as a secondary outcome. A combined analysis of studies that used high-dose vitamin D supplementation (approximately 1000 IU/d) found a 10% reduction in cardiovascular events, but this reduction was not statistically significant (RR 0.90, 95% CI 0.77 to 1.05). When studies that combined vitamin D plus calcium supplementation were included, there was no trend toward a benefit (RR 1.04, 95% CI 0.92 to 1.18).

COVID-19

SYSTEMATIC REVIEWS

A 2021 Cochrane systematic review evaluated vitamin D supplementation for the treatment of COVID-19.[37] The review included three RCTs with a total of 356 participants, 183 of whom were received vitamin D treatment. Two of these studies (n=313) assessed mortality in patients with moderate to severe disease, with no statistically significant differences found. One study (n=237) reported data on the need for invasive mechanical ventilation and found that 9 of 119 participants treated with vitamin D needed invasive mechanical ventilation, compared to 17 of 118 participants receiving placebo (RR 0.52, 95% CI 0.24 to 1.13). The authors concluded that “[t]here is currently insufficient evidence to determine the benefits and harms of vitamin D supplementation as a treatment of COVID-19. The evidence for the effectiveness of vitamin D supplementation for the treatment of COVID-19 is very uncertain. Moreover, we found only limited safety information, and were concerned about consistency in measurement and recording of these outcomes.”

DEPRESSION

SYSTEMATIC REVIEWS

A meta-analysis by Wang (2024) included 18 RCTs that evaluated vitamin D supplementation on primary depression.[38] The results indicated that supplementation was associated with significantly reduced depressive symptom scores only in patients with serum 25(OH)D levels higher than 50 nmol/L.

Gowda (2015) published a meta-analysis of RCTs evaluating the effect of vitamin D supplementation in reducing depressive symptoms.[39] A total of nine trials were included in the review with a total of 4,923 patients who were diagnosed with depressive disorder based upon the Diagnostic and Statistical Manual of Mental Disorders or other symptom checklist for depression. No significant reduction in depression related symptoms was observed with vitamin D supplementation compared to no supplementation. The study was limited by inclusion of patients with adequate vitamin D serum levels at baseline. In addition, vitamin D doses and intervention duration varied among included studies.

Authors of the IOM report conducted an extensive systematic review to clarify the benefits of vitamin D supplementation for a variety of indications.[7] For depression, five RCTs on general depression and seasonal affective disorder were identified. The shorter, smaller studies[40-42] reported some improvement in mood with increased vitamin D supplementation, while the longer, larger studies[43] showed no improvements. The IOM committee concluded the findings were inconsistent and “few or no clinical trials were identified to support biological plausibility. As a result of the many shortcomings in study design and quality of observational evidence and the paucity of high-quality evidence from RCTs identified by the committee, the findings for neuropsychological indicators are inconclusive.”

Li (2013) evaluated the efficacy of oral vitamin D supplementation on depression.[44] A total of six RCTs containing 1,203 patients (72% female, 71 depressed patients) were selected for inclusion. Five of the studies evaluated adults at risk for depression while one study evaluated the effects of vitamin D on patients with depression. Authors noted that the quality of evidence was low. A classic and Bayesian meta-analysis demonstrated no significant effect of vitamin D supplementation on postintervention depression scores compared to the placebo group. In addition, no differences were demonstrated in subgroup or sensitivity analyses.

The 2012 Washington State Health Care Authority Health Technology Assessment (WA TEC)[9] concluded that although current evidence suggested an association between vitamin D deficiency and mood disorders, including depression, there were no studies which provided support for a causal relationship between vitamin D and mood disorders.

Additional systematic reviews[45] reported an association between depression symptoms and vitamin D deficiency when compared to healthy controls; however, the effect of vitamin D supplementation on patients with depression was not assessed. Therefore, the clinical utility of testing and treating for vitamin D deficiency was not established. Also, reviews of published studies regarding vitamin D treatment to prevent or treat depression have been published;[46] however, these reviews are based upon nonrandomized trials and are therefore not considered reliable for establishing the clinical utility of vitamin D testing or treatment for depression.

RANDOMIZED CONTROLLED TRIALS

Kjaergaard (2012) assessed the effect of vitamin D treatment on depression scores in participants with both low and high 25(OH)D levels.[47] Participants with low 25(OH)D levels (n=230) were randomized to either placebo or 40,000 IU of vitamin D/week for six months. Those with high 25(OH)D levels (n=114) were used as nested controls. The Beck Depression Inventory, Hospital Anxiety and Depression Scale, Seasonal Pattern Assessment Scale and Montgomery-Åsberg Depression Rating Scale were all used to evaluate depressive symptoms. Although depression was found to be associated with lower vitamin D levels, no differences were observed in depressive symptoms with vitamin D treatment compared to placebo.

The Women's Health Initiative (WHI) Calcium and Vitamin D (CaD) trial included postmenopausal women aged 50 to 79 years in a large, randomized trial evaluating the effect of vitamin D treatment on depression symptoms.[22] Exclusion criteria did not include recent history of vitamin D supplementation and women were allowed to continue personal use of vitamin D and calcium supplementation throughout the study. Participants in the treatment group (n=18,176, total n=36,282) received 1,000 mg of calcium and 400 IU of vitamin D daily for three years. The Burnam scale was used to assess depressive symptoms at baseline and annually. Ultimately, authors reported no significant differences in the risk for depression between groups. This study was limited by a 63% adherence rate reported at the three-year follow-up. In addition, mean baseline depression scores were low, suggesting most participants were not experiencing clinically relevant depression at the start of the study.

Sanders (2011) conducted a double-blind, randomized, placebo-controlled trial to examine the effects of high-dose vitamin D on mood in women aged 70 or older.[48] Participants who were taking vitamin D supplementation were excluded leaving approximately 2,260 to be randomized. Active control groups were instructed to take a single dose of 500,000 IU vitamin D3/annually during the autumn/winter months for three to five years. Participants were asked to complete the General Health Questionnaire (GHQ) at three time points during the study (baseline, 12- and 15-months post-dose). In addition, a subset of 150 participants, randomly chosen from both groups, completed additional questionnaires and blood sampling to determine serum 25D levels at baseline and post-dose time points. Serum samples were not otherwise collected in the general study participants. Ultimately no differences were observed in either the general or nested studies. Despite a measured increase in 25D levels from low to normal in the nested treatment group, no changes in mood or depression status were observed compared to the control group.

In another large randomized study of older women (70 years or older), Dumville (2006) evaluated the effects of vitamin D supplementation as a prevention of seasonal affective disorder (SAD), a sub-type of depression.[49] A total of 2,117 women were randomized to receive 800 IU of vitamin D daily with calcium or placebo between the months of May and October. Only 1,621 (77%) participants completed both baseline and six-month SF-12 questionnaires. At the six-month follow-up, no significant difference was observed between groups in mental health scores. Serum measures and pre-study vitamin D levels and supplementation were not reported.

In an RCT by Jorde (2008), the effect of vitamin D supplementation was evaluated on symptoms of depression in 441 overweight subjects.[50] Subjects were randomized to one of three groups: group DD received 40,000 IU of vitamin D, group DP received 20,000 IU of vitamin D and group DD received a placebo per week, over the course of one year. Participant depression scores were measured by the Beck Depression Inventory (BDI) questionnaire at baseline and 12 months. Serum blood samples were drawn at baseline and every three

months during the study. During the course of the study, no significant changes or differences were observed regarding weight and physical activity in either group. A significant improvement in BDI scores was reported in both treatment groups; however, authors were unable to control for confounding factors which may have influenced these findings such as age, sex, smoking, and other medications or medical conditions. For example, the placebo group had a higher number of non-smoking males with higher BMIs. In addition, there was a high (over 22%) drop-out rate which calls into question conclusions reached by this study.

DIABETES

SYSTEMATIC REVIEWS

Thompson (2017) published an evidence-based review to serve as a resource for the management of comorbidities associated with childhood overweight and obesity.[51] Authors conducted a narrative review of 35 studies published between January 2010 and January 2015, and vitamin D deficiency recommendations were based on Level II evidence ([a] randomized controlled and [b] nonrandomized trials). The care algorithm included serum 25(OH)D testing for children aged 2 to 18 years with BMI ≥ 85th percentile. However, treatment was recommended as either brief daily unprotected sun exposure, or a combination of sun exposure and vitamin D2 or D3 supplementation depending on serum testing results. Limitations have previously been described (see Background, above) regarding uncertainty for optimal cutoff values in testing, and performance of the testing diagnostic. Overall, this resource statement was limited by availability of high-quality evidence as stated by the authors.

In the 2010 Institute of Medicine (IOM) summary regarding vitamin D treatment in patients with diabetes, the committee found that studies associating type 2 diabetes with vitamin D deficiency were unable to control for confounding factors such as weight and obesity, which predispose individuals to lower vitamin D levels.[7] The committee found no randomized controlled trials regarding vitamin D treatment and type 1 diabetes. Overall, the IOM report concluded that, “(e)vidence from RCTs on the effect of vitamin D supplements on incident diabetes or markers of glucose homeostasis is variable, and few RCTs showing significant results were identified.” The review committee concluded that there was insufficient evidence to support a role for vitamin D in the production of insulin and as a modulator of pancreatic endocrine function.

The WA TEC report concluded that evidence considered from three RCTs found no evidence to suggest that vitamin D treatment had a positive effect on the incidence of diabetes or diabetes markers in adults.[9]

Haroon (2015) published results of a meta-analysis of seventeen RCTs and seven nonrandomized trials assessing the effect of vitamin D supplementation upon glycemic control in patients type 2 diabetes.[52] Authors concluded the current evidence did not demonstrate any long-term symptom improvement upon hyperglycemia with vitamin D supplementation.

George (2012) conducted a systematic review and meta-analysis which evaluated the effect of vitamin D supplementation on fasting glucose, glycemic control, insulin resistance, insulin/C-peptide levels, micro- and macrovascular outcomes, and progression from non-diabetes to diabetes.[53] Data was pooled from 15 RCTs, and authors reported no significant difference in fasting glucose, HbA1C or insulin resistance in the treatment group compared to the placebo group. There was insufficient data to draw conclusions regarding micro- and macrovascular

events. Authors concluded that there is, “currently insufficient evidence of beneficial effect to recommend vitamin D supplementation as a means of improving glycaemia or insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance.”

Additional reviews of published studies regarding vitamin D supplementation to prevent or treat type 2 diabetes have been published;[54-60] however, these reviews are based upon non-randomized prospective studies and are therefore not considered reliable for establishing the clinical utility of vitamin D testing or treatment in these patients.

RANDOMIZED CONTROLLED TRIALS

Several RCTs have been published since the IOM summary and are reviewed below. A single RCT was identified regarding vitamin D treatment in patients with type 1 diabetes.

Virtanen (2025) published the results of an RCT evaluating the effects of vitamin D supplementation on the incidence of type 2 diabetes in a generally healthy older adult population in Finland.[61] This five-year, placebo-controlled trial randomized 2,271 adults aged 60 to 56, into one of three parallel arms: placebo control, 1600 IU/day of vitamin D3, or 3200 IU/day of vitamin D3. After 4.2 years of follow-up, there were no significant differences between groups in the risk of developing diabetes. A smaller subcohort of the participants (n=505) had additional data collected, and at 24-months follow-up, no differences in plasma glucose, insulin concentration, BMI, or waist circumference were seen between groups in this subcohort.

Bizzarri (2010) evaluated whether calcitriol, the active form of vitamin D, supplementation had any effect on beta-cell function and glycemic control in recently diagnosed type 1 diabetes patients.[62] A total of 34 patients were randomized to receive 0.25 microg/daily calcitriol or placebo for 24 months. No significant differences were observed in HbA1C or c-peptide levels between groups. Although the study follow-up period was sufficient, the number of subjects recruited was small which may limit any conclusions reached in this study. Ultimately, authors concluded that the doses of calcitriol used were ineffective in effecting glycemic control or beta-cell function.

de Zeeuw (2010) conducted the VITAL study, a multi-national study regarding the effect of paricalcitol supplement (the active form of vitamin D) on albuminuria in type 2 diabetic patients with nephropathy.[63] A total of 281 patients were randomized into one of three groups: 1 ug/daily paricalcitol, 2 ug/daily paricalcitol or placebo for 24 weeks. Authors reported that patients on 2 µg paricalcitol showed a nearly sustained reduction in urinary albumin-to-creatinine ratio (UACR), ranging from –18% to –28% (p=0.014 vs placebo). However, UACR reduction levels did not reach a significant change from baseline (p=0.053) and the 2 ug group had a significantly higher drop-out rate compared to the 1 ug and placebo groups. Ultimately, authors did not demonstrate that these effects prevented progression of renal failure in this patient population, and several additional authors recommended longer follow-up and evaluation of additional study end-points.[64-67]

Yiu (2013) studied the effect of vitamin D supplementation on endothelial dysfunction and cardiovascular disease in 100 type 2 diabetes patients[68] for 12 weeks. Although significant increases in serum 25(OH)D levels were observed in the treatment group, no difference was observed in vascular function or inflammation between groups.

Harris (2012) examined the effects of vitamin D treatment on insulin sensitivity and glycemia in

89 overweight African Americans for 12 weeks.[69] Again, a significant increase in 25(OH)D levels was observed; however, this change did not impact post-load glucose or other measures of glycemia compared to the placebo group.

Shab-Bidar (2012) evaluated the effects of a vitamin D-fortified yoghurt drink (doogh) on systematic inflammation biomarkers in 100 patients with type 2 diabetes[70] for 12 weeks. Significant improvements in inflammatory biomarkers were observed in the treatment group compared to those receiving the placebo; however, authors did not demonstrate how these changes translated into an improvement in symptoms or resolution of diabetes.

Mitri (2011) examined the effects of vitamin D supplementation on glucose homeostasis in 92 adults at high risk for diabetes.[71] Patients randomized to the treatment group received 2000 IU/ of vitamin D daily for 16 weeks. A significant improvement in pancreatic β cell function was observed in the treatment group compared to the placebo group; however, there was no significant improvement in HbA1C levels between groups.

Additional studies were identified which indicated some improvement in various serum levels associated with type 2 diabetes;[72-80] however, similar to the previously reviewed RCTs, these studies were limited by small sample size (n<100), short-term follow-up and/or potential confounding factors which could have influenced outcomes. In addition, the doses of vitamin D administered to the treatment groups varied among studies, calling into question the optimal level of supplementation required for this population. Additional studies which found no improvement in diabetes symptoms with vitamin D supplementation were also identified.[81-83]

A Mendelian randomization study was published by Manousaki (2021), evaluating the impact of genetically decreased vitamin D levels on the development of type 1 diabetes.[84] Single nucleotide polymorphisms (SNPs) that were strongly associated with 25(OH)D levels in a large European genome-wide association study (GWAS) were assessed in a meta-analysis of 12 type 1 diabetes GWAS studies (9,358 cases and 15,705 controls). There was no significant association found between genetically reduced 25(OH)D levels and diabetes incidence in the populations studied. This finding is consistent with a lack of a causal role for vitamin D in the development of this disorder.

FATIGUE AND PAIN

The principal outcomes associated with treatment of fatigue or pain due to any cause may include relief of fatigue or pain, improved functional level, and return to work. Relief of these indications is a subjective outcome that is typically associated with a placebo effect. Therefore, data from adequately powered, blinded, RCTs are required to control for the placebo effect, determine its magnitude, and determine whether any treatment effect from vitamin D supplementation provides a significant advantage over the placebo.

SYSTEMATIC REVIEWS

No evidence-based systematic review or meta-analysis of RCTs regarding vitamin D supplementation for either generalized pain, myofascial pain, bone pain, chronic pain or fatigue were identified.

RANDOMIZED CONTROLLED TRIALS

Schreuder (2012) evaluated vitamin D supplementation on non-specific musculoskeletal complaints in 84 vitamin D-deficient (defined as a 25(OH)D level of less than 50 nmol/L) non-

Western immigrants in a semi-crossover randomized trial.[85] Patients randomized to the treatment group received 150,000 IU vitamin D at baseline; at six weeks participants in this group were then randomized again to receive a second dose or placebo. Patients in the placebo group all received vitamin D treatment at six weeks. Pain was assessed using a visual analogue scale (VAS) and by marking pain sites on a mannequin. Pain medication and physical therapy were reported to be similar between groups. At six weeks, a significant difference in pain reduction was reported in patients receiving vitamin D treatment (34.9% vs. 19.5%, p=0.04). In order to assess the durability of any treatment effects, larger, long-term studies are needed that control for the sample heterogeneity, continued use of pain medication and physical therapy. In addition, this study is limited by a relatively small sample size given the prevalence and causes of non-specific musculoskeletal pain.

Björkman (2008) conducted a RCT of 216 elderly, long-term care patients to evaluate the treatment of vitamin D on reported symptoms of pain.[86] Patients were randomized to receive 0, 400, or 1200 IU cholecalciferol/day for six months. Pain was measured by the Resident Assessment Instrument (RAI), Discomfort, Behavior Scale, and Pain Assessment in Advanced Dementia Scale. Although a marked increase in 25(OH)D levels was observed in the treatment groups, no significant difference was reported in pain levels compared to the placebo group. Authors concluded that, “vitamin D deficiency was not associated with pain or pain behavior.”

Additional studies reported on the use of vitamin D supplementation as a treatment for pain or fatigue in patients with a variety of conditions such as: nonspecific low back pain, cancer, multiple sclerosis, menopause and fibromyalgia. In many of these studies, no significant difference between groups was observed.[87-94] In addition, these and other studies suffered from methodological limitation such as: small sample size[87, 89, 95-98] (n<100), short-term follow-up (less than one year)[89, 95-98], or inclusion of participants who did not have vitamin D deficiency at the start of the study.[88, 89, 96, 98, 99] It is also worth noting that dose levels and frequency of dosing varied drastically across all studies, calling into question any conclusions regarding optimal dosing strategies in patients with pain or fatigue.

FIBROMYALGIA

SYSTEMATIC REVIEWS

In a systematic review by Daniel (2011), evidence regarding and association between vitamin D deficiency and fibromyalgia was assessed to determine whether vitamin D testing and subsequent treatment is warranted.[100] Ultimately authors concluded that evidence establishing an association between vitamin D deficiency and fibromyalgia is inconclusive. The identified RCTs demonstrated no association between vitamin D and relief of pain associated with fibromyalgia; nonrandomized trials were inconclusive regarding an association. The single adequately powered RCT identified, suggested supplementation did not improve pain related to fibromyalgia.

RANDOMIZED CONTROLLED TRIALS

Other than the trial noted in the systematic review by Daniel (2011) above, no RCTs regarding vitamin D treatment and fibromyalgia were identified.

HYPERLIPIDEMIA

SYSTEMATIC REVIEWS

Wang (2012) published a meta-analysis of RCTs evaluating the effects of vitamin D treatment on blood lipids.[101] A total of 12 RCTs were identified and data from 1,346 participants were pooled. The primary outcome measures were changes in total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL) and triglycerides (TG) from baseline. No significant differences were observed in any of the study measurements. The authors of this study called for additional, large-scale trials with adequate doses and appropriate population selection to help determine the efficacy of vitamin D treatment on lipid profiles.

RANDOMIZED CONTROLLED TRIALS

Ponda (2012) examined whether oral vitamin D supplementation improved the lipid profile of 150 vitamin D-deficient (defined as 25(OH)D <20 ng/mL) adults with cardiovascular disease.[102] Patients were randomized into either the treatment group which received 50,000 IU of vitamin D3 weekly for eight weeks or placebo. No changes to the lipid profile were observed in the treatment group compared to the placebo group. Authors concluded that short-term correction of a 25-hydroxyvitmain D deficiency did not improve lipid profiles.

Wood (2012) evaluated vitamin D treatment on conventional cardiovascular disease (CVD) markers in 305 healthy post-menopausal women.[103] Patients were randomized to receive 400 or 1000 IU vitamin D3 daily or placebo for one year. Primary outcomes were serum lipid profile (total cholesterol, HDL, LDL, triglycerides, and apolipoproteins A-1 and B100), insulin resistance (homeostatic model assessment-insulin resistance, HOMA-IR), inflammatory biomarkers (high-sensitivity C-reactive protein, IL-6, soluble intracellular adhesion molecule-1), and blood pressure. A total of 265 (87%) of patients completed the study and no difference in any lipid marker in the treatment group compared to the placebo group was observed. Authors concluded that improvements in vitamin D status were unlikely to reduce markers related to CVD.

Muldowney (2012) examined the effects of cholecalciferol on a variety of biomarkers for cardiovascular disease, including serum 25(OH)D, intact parathyroid hormone, systolic and diastolic blood pressure, fasting lipids, glucose and insulin, HOMA-IR, high-sensitivity C-reactive protein, matrix metalloproteinase-9, and its inhibitor (tissue inhibitor metalloproteinase-1).[104] Patients from two studies, one with patients aged 20 to 40 years (n=202) and the other with patients under age 65 (n=192), were randomized to receive 0, 5, 10, or 15 µg/d (0-600 IU) doses of cholecalciferol during wintertime. Measurements were taken at baseline and then again at 22 weeks. There were no reported differences in either age group between the treatment and control group.

Heikkinen (1997) evaluated the effects of vitamin D supplementation and hormone replacement therapy (HRT) on serum lipids in 464 postmenopausal women.[105] Subjects were randomized into one of four groups: HRT (sequential combination of 2 mg estradiol valerate and 1 mg cyproterone acetate), Vit D3 (vitamin D3 300 IU/day), HRT+Vit D3 (both as above), or placebo (calcium lactate 500 mg/day) for three years. Concentrations of serum cholesterol, LDL, HDL and triglycerides were measured at baseline, 12, 24 and 36 months. Over the course of the study 76 (16.4%) women dropped out; with 57 of them dropping out of the HRT and HRT+Vit D3 groups. Data from the 320 women who completed the study indicated that serum concentrations of LDL cholesterol decreased in the HRT group (10.1%, p<0.001) and the HRT+Vit D3 group (5.9%, p=0.005), increased in the Vit D3 group (4.1%, p=0.035) but remained unchanged in the placebo group. Total cholesterol decreased slightly in both the

HRT and HRT+Vit D3 groups, but not in the other two groups. The HDL:LDL ratio decreased in the vitamin D3 group (10.5%, p<0.001) and triglycerides increased slightly in all groups. These results suggest that pure vitamin D3 treatment may have a negative effect on lipids in postmenopausal women taking HRT; however, the loss-to-follow-up rate was high, limiting conclusions reached in this study.

Additional, short-term randomized trials which include varying dose levels of administered vitamin D were identified which showed no difference between treatment and placebo groups for multiple cardiovascular disease risk markers.[106-117]

HYPERTENSION

SYSTEMATIC REVIEWS

A systematic review by Farapti (2020) evaluated the effect of vitamin D supplementation on blood pressure in elderly patients (age ≥60 years).[118] Twelve RCTs were included in the review and meta-analysis, and the mean age of participants was 65.5 years. The RCTs varied in their included populations, and some participants had hypertension while others did not. Most of the included studies were reported to have a low risk of bias. While the results of the meta-analysis indicated that vitamin D supplementation was associated with greater changes in serum 25(OH)D concentrations, no effect was seen for changes in systolic or diastolic blood pressure.

The WA TEC report concluded that evidence from a single meta-analysis of seven small RCTs may suggest some small clinically meaningful reduction in systolic blood pressure with vitamin D treatment and an uncertain effect on diastolic blood pressure.[9]

Wu (2010) conducted a meta-analysis to evaluate the use of vitamin D supplements on blood pressure reviewing only double-blind RCTs of oral vitamin D in normotensive or hypertensive patients.[119] Of the 244 studies reviewed, only four met inclusion criteria. Data from 429 patients were pooled. A statistically significant reduction in systolic blood pressure (SBP) was observed in patients treated with vitamin D compared to placebo 2.44 mmHg (weighted mean difference [WMD] -2.44, 95% CI -4.86 to -0.02). No reduction was observed in diastolic blood pressure compared to placebo. Study authors note the need for additional RCTs in order to determine the effects of vitamin D supplementation on patients with hypertension.

Witham (2009) conducted a systematic review and meta-analysis to determine the effects of vitamin D supplementation on blood pressure in patients with hypertension.[120] A total of 11 small RCTs with variable methodological quality were included in the review. A meta-analysis was performed on eight studies where patient baseline blood pressure was more than 140/90 mmHg. From that meta-analysis a small statistically significant reduction in diastolic blood pressure of -3.1 mmHg was reported in the treatment group. No other significant differences were observed between groups.

In the previously mentioned Elamin (2011) review of vitamin D treatment on cardiovascular outcomes, pooled analysis of RCTs included data on systolic or diastolic blood pressure from 767 patients.[33] No significant difference between treatment and control groups was reported.

Kunutsor (2014) evaluated the effects of vitamin D supplementation on SBP and diastolic blood pressure (DBP).[121] Sixteen randomized trials were included in the analysis which showed no significant reduction in SBP (-0.94, 95% CI -2.98, to1.10 mmHg) and DBP (-0.52,

95% CI -1.18 to 0.14 mmHg). In addition, authors noted there was significant heterogeneity and publication bias among SBP trials.

Additional reviews of published studies regarding vitamin D supplementation to prevent or treat hypertension have been published;[122-127] however, these reviews either showed no benefit with supplementation[128] or were based upon non-randomized prospective studies and are therefore not considered reliable for establishing the clinical utility of testing and treatment in patients with hypertension.

RANDOMIZED CONTROLLED TRIALS

In the previously mentioned Women's Health Initiative (WHI) Calcium and Vitamin D (CaD) trial, data were analyzed to determine the effect of vitamin D treatment on blood pressure and the incidence of hypertension in postmenopausal women.[129] Over 17,122 hypertensive women were randomized and to either vitamin D treatment or placebo and followed for seven years. Data from this study found no reduction in either blood pressure or the risk of developing hypertension in patients taking vitamin D compared to those taking placebo.

In a follow-up analysis from the previously mentioned study by Jorde (2010), data were evaluated to determine the effect of vitamin D supplementation on cardiovascular risk markers in 330 overweight and obese patients.[110] A slight increase in systolic blood pressure was observed in the treatment group receiving 20,000 IU per week of vitamin D compared to placebo. Otherwise, no significant differences were observed in blood pressure measures between the treatment and placebo groups.

Additional trials were identified which showed no difference between treatment and placebo groups for vascular health disease risk markers.[114, 117, 130-134]

MORTALITY

SYSTEMATIC REVIEWS

A systematic review of RCTs by Peng (2020) evaluated the role of vitamin D supplementation on mortality in critically ill patients.[135] Eligibility criteria included adults admitted to the intensive care unit who received any administration of vitamin D. In a meta-analysis of nine trials (n=2,066), vitamin D administration was not associated with all-cause mortality at any time point (30 days, 60 days, 180 days, or longest follow-up).

Avenell (2016) published an update of a 2010 Cochrane Systematic Review regarding nutritional supplementation for hip fracture aftercare in older people.[136] Reviewing 41 trials through November 2015 (including 3,881 total participants), the authors pooled outcome data when possible. Interventions included multinutrient supplements (providing non-protein energy, protein, vitamins and minerals) given orally, enterally or intravenously, compared with supplements containing less or none of these components, or no treatment. Placebo controlled trials, and trials comparing various doses, or comparison to no treatment were included. Only one study of vitamin D was included, though not part of the primary outcome analysis. The study compared use of D3 (1000 IU/d) and calcium carbonate (600 mg/d) to vitamin D2 (1000 IU/d) and an equivalent dose of calcium carbonate over three months; however, incomplete outcome data were available. The authors found low-quality evidence that oral multinutrient supplements (all supplements) started before or soon after surgery may prevent complications within the first 12 months after hip fracture, but that they have no clear effect on mortality.

Zheng (2015) published a meta-analysis assessing high-dose intermittent vitamin D supplementation on falls, fractures and mortality among older adults.[137] Nine randomized trials were included in the analysis. Intermittent, high-dose vitamin D supplementation did not reduce all-cause mortality or prevent falls or fractures.

Schottker (2014) assessed the association of serum 25(OH)D in all-cause, cardiovascular and cancer related mortality.[138] Large consortium cohort studies were utilized and 26,018 patients, ages 50 to 79, were included. Serum concentrations from the highest quintile were compared to the lowest quintile. Low serum concentrations were associated with increased risk for all-cause mortality (RR 1.57) and for cardiovascular mortality in patients with (RR 1.70) and without a history of cardiovascular disease (RR 1.41). In addition, low serum levels were associated with an increased risk for cancer-related mortality in patients who had previously had cancer (RR 1.70).

In a similar study, Chowdhury (2014) evaluated the association of vitamin D and all-cause, cardiovascular and cancer related mortality.[139] Authors included data from 73 nonrandomized (849,412 participants) and 22 RCTs (vitamin D given alone vs. placebo or no treatment; 30,716 participants). Baseline bottom versus top third vitamin D levels were compared and lower third vitamin D levels were associated with cardiovascular mortality (RR 1.35), cancer mortality (RR 1.14) and all-cause mortality (RR 1.35) when compared to the top third. However, this study did not evaluate whether vitamin D supplementation had any impact upon mortality risks in patients with low serum levels.

Additional reviews were identified which demonstrated an association between vitamin D levels and mortality risk;[140-143] however, the analysis included nonrandomized studies and included studies which were heterogenous in nature, contained significant outcome reporting bias and did not evaluate the impact of supplementation upon improved health outcomes.

RANDOMIZED CONTROLLED TRIALS

Appel (2021) published the results from the STURDY Collaborative Research Group, a large (n=688) RCT evaluating four doses of vitamin D in individuals at least 70 years of age at elevated fall risk and a serum vitamin D level of 25 to 72.5 nmol/L.[144] The primary outcome was time to first fall or death over two years. The primary outcome during the confirmatory stage was not significantly different between those receiving the control dose of vitamin D (200 IU/day) and those receiving what was considered the optimal dose of 1000 IU/day. Doses of 1000 IU/day or greater were associated with safety concerns. The study is limited by the use of vitamin D 200 IU/day as a control group rather than use of a placebo.

MULTIPLE SCLEROSIS

SYSTEMATIC REVIEWS

At least four systematic reviews have examined the effect of vitamin D supplementation in patients with multiple sclerosis (MS).[145-148] Authors described six RCTs, all of which were small (n<100). Patient follow-up ranged from six months to two years, and dosing and administration of vitamin D varied. None of the trials reported improvement in MS relapse rates; most trials showed no effect of vitamin D on any of the surrogate or clinical outcomes. Only one trial reported improvement in magnetic resonance imaging of lesions in the vitamin D supplementation group.

The 2007 Agency for Healthcare Research and Quality (AHRQ) report evaluated the evidence related to MS and vitamin D and found only case-controlled, non-randomized trials.[6] In many of these studies an association was found between MS and lower levels of vitamin D; however, no study was identified which demonstrated the effect of vitamin D treatment on symptoms of MS or overall improvement of the condition.

The IOM report found only observational non-randomized studies with conflicting conclusions regarding an association between vitamin D deficiency and MS. The IOM report concluded that, “The lack of causal evidence further diminishes the likelihood for a relationship between vitamin D and MS.”[7]

The WTA TEC report reviewed evidence from three RCTs and concluded, “There was insufficient evidence regarding a link with the risk of obesity, gestational diabetes, multiple sclerosis (MS), or depression and mood disorders; for these outcomes, there was no evidence from longitudinal studies or very sparse evidence.”[9]

RANDOMIZED CONTROLLED TRIALS

A phase 2, double-blind trial by Hupperts (2019) randomized 229 relapsing-remitting MS patients to receive subcutaneous interferon-β-1a plus either a placebo or high-dose vitamin D3 three times per week.[149] After 48 weeks, there was no difference in the primary outcome (no evidence of disease activity, NEDA-3) between groups.

PREGNANCY

SYSTEMATIC REVIEWS

A Cochrane systematic review on vitamin D supplementation and pregnancy was published by Palacios (2019)[150] and updated in 2024[151]. In the 2019 review, Vitamin D supplementation during pregnancy was found to probably reduce the risk of pre-eclampsia (moderate-certainty evidence), gestational diabetes (moderate-certainty evidence), severe postpartum hemorrhage (low-certainty evidence), and low birth weight in infants (moderate-certainty evidence). However, not all studies measured baseline 25(OH)D levels and analyses based on initial 25(OH)D concentrations were not performed. Most studies were considered to have a low-moderate risk of bias. In the 2024 update, a trustworthy assessment tool removed most of the studies that were previously included in the 2019 review. In the updated analyses, the evidence was very uncertain about Vitamin D supplementation for the outcome of pre-eclampsia (very low certainty evidence), gestational diabetes (very low certainty evidence), and pre-term birth (very low certainty evidence). However, the authors found that supplementation with Vitamin D during pregnancy may reduce the risk of severe postpartum hemorrhage (low-certainty evidence) and low birth weight (low-certainty evidence). The risk of bias was high for blinding in four studies and for attrition in four studies. Additionally, not all studies measured baseline 25(OH)D levels.

A systematic review and meta-analysis by Gallo (2020) included 20 RCTs on the effects of maternal vitamin D supplementation on pregnancy outcomes.[152] While there was some evidence that vitamin D was associated with a decreased maternal HOMA-IR, based on data from five studies, no effect was seen for other maternal or infant outcomes, including preeclampsia, cesarean section, gestational age, and birth length.

Khaing (2017) conducted a systematic review and network meta-analysis of RCTs with the aim of comparing the effects of calcium, vitamin D, both supplements, or neither on preeclampsia and gestational hypertension (GH) or pregnancy induced hypertension (PIH).[153] Search strategy, study selection, data extraction, and risk of bias assessment were transparent and well-described. The study was conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA), extension of network meta-analyses, and the review protocol was registered with the international prospective register of systematic review (PROSPERO number CRD42015025389). A total of 27 RCTs were included in quantitative analysis. Among these, 19 studies (n=26,299) compared calcium vs. placebo, three studies (n=357) compared vitamin D vs. placebo, four studies (n=1,169) compared calcium plus vitamin D vs. placebo, and one study (n=175) compared calcium plus vitamin D vs. calcium. Risk of bias could not be assessed in three studies; of the remaining studies, half had low risk of bias for selective outcome reports, and most studies (16/24) reported double blinding. Pooled analysis found vitamin D reduced preeclampsia when compared to placebo in three RCTs (n=203 vs. 154), with a pooled RR of 0.47 (95% CI 0.24 to 0.89). Network meta-analysis was performed for indirect comparison and found vitamin D alone could reduce risk of preeclampsia by 57% when compared to placebo, though was not statistically significant (pooled RR of 0.43, 95% CI 0.17 to 1.11). Heterogeneity and small study effects were evaluated and deemed to be insignificant. However, there were limited data to pool for vitamin D supplementation vs placebo, and additional larger studies are warranted to make conclusions about clinically significant effects.

Roth (2017) reported results from a systematic review of RCTs implementing prenatal vitamin D (vitamin D2 or D3, any dose) administration.[154] Trials used placebo, no vitamin D, or vitamin D ≤ 600 IU/day. Using transparent study inclusion and evaluation criteria, 43 trials from 77 publications (total n=8,406) were included for meta-analysis and were graded for risk of bias according to the Cochrane Collaboration tool. Pooled RRs (dichotomous outcomes) and weighted mean differences (continuous outcomes) were calculated with 95% confidence intervals; missingness was appropriately accounted for, and sensitivity analyses were conducted. Both maternal, and infant/childhood outcomes were analyzed. Vitamin D increased maternal/cord serum concentration of 25(OH)D, but the dose-response effect was weak; maternal clinical outcomes were rarely ascertained or reported, and the available data did not provide evidence of benefit. Authors found strong evidence that prenatal vitamin D reduced the risk of offspring wheeze by age three years (0.81, 95% CI 0.67 to 0.98, two comparisons). Additionally, vitamin D supplementation contributed to increased mean birth weight 58.33 g (95% CI 18.88 g to 97.78 g, 37 comparisons), reduced risk of small for gestational age RR 0.60, 95% CI 0.40 to 0.90, seven comparisons, and increased infant length at one year (weighted mean difference 1.30, 95% CI 0.54 to 2.06). These outcomes were not robust in sensitivity and subgroup analysis. Only 8 of 43 trials were found to have low risk of bias; overall the studies were small and of low quality. The authors concluded that additional trials are needed to inform clinical or policy recommendations, particularly with well-designed endpoint data collection.

RANDOMIZED CONTROLLED TRIALS

Other than the trials reviewed in the systematic review above, and the RCT of prenatal supplementation in 881 pregnant women at high risk of having children with asthma (2016) summarized in the Asthma and Wheezing section above,[23] no additional RCTs regarding vitamin D treatment and pregnancy were identified.

PSORIASIS

The majority of published evidence regarding vitamin D treatment for skin diseases is focused on first-line topical treatment options for psoriasis.[155-159] There is a vast body of both RCTs and systematic reviews evaluating vitamin D analogue therapy for psoriasis. In addition, the American Academy of Dermatology lists vitamin D analogues as a topical treatment option for patients with psoriasis.[160] However, recent meta-analyses do not demonstrate that vitamin D analogue therapy is superior to topical corticosteroid treatment. Many of the randomized studies combine the two therapies, which limit conclusions regarding the effect of vitamin D-based topical treatment. Despite this evidence, vitamin D analogue therapy has become an established treatment for psoriasis; however, it is not established that vitamin D testing is required or routinely performed when choosing this therapy. No published, peer-reviewed evidence was identified which evaluated vitamin D analogue therapy in patients with vitamin D deficiency. In addition, no studies were identified which included vitamin D testing as part of the study design, suggesting an evaluation of vitamin D levels is not an essential component of treatment decision-making or treatment success in patients with psoriasis.

VITAMIN D SCREENING IN HEALTHY POPULATIONS

Vitamin D screening is often performed in healthy patients as a preventive measure, usually as part of a routine wellness exam.

SYSTEMATIC REVIEWS

Evidence which focused on the effects of vitamin D supplementation in relation to general risks for deficiency, such as age or geographic location, was identified; however, there were numerous gaps in the data concerning the impact of routine screening in these populations.

The current gaps are discussed in several major evidence reports:

It is not clear how vitamin D test results guide treatment decisions differently compared to decisions that would be made in the absence of test results.

The IOM report concluded that the benefits of vitamin D for conditions not related to bone health, conditions which were often spotlighted in the media,[161] "…were from studies that provided often mixed and inconclusive results and could not be considered reliable."[7] However, the IOM and other evidence reports highlighted the importance of maintaining an average range requirement of vitamin D and calcium across the general population, as a means of avoiding deficiency and ensuring optimal bone health. Given the conclusions reported in the WTA TEC assessment, that a substantial proportion of patients across all populations were vitamin D deficient, routine supplementation without screening was suggested for certain populations.[9] In recognition that all people require a sufficient level of vitamin D, the IOM committee issued age-based dietary reference intakes that included, "Estimated Average Range Requirements (EAR)s and the Recommended Dietary Allowances (RDA), that are intended to serve as a guide for good nutrition and to provide the basis for the development of nutrient guidelines in both the United States and Canada." [7] The IOM recommendations are intended to suit the needs of nearly all people and are proposed as a guide for daily supplementation. For the purposes of daily vitamin D maintenance in the general population, testing is not required, as patients may choose to follow the general IOM vitamin D intake guidelines based on age and/or condition. In addition, serum measurements are often rendered uninformative due to invalidated cut-off points and unreliable test results,

leaving providers and patients to choose whether or not to follow recommended supplementation guidelines.

A 2021 updated evidence review from the United States Preventative Service Task Force (USPSTF) included a pooled analysis of eight RCTs evaluating vitamin D treatment in community-dwelling adults (n=2,006) that found no difference between groups for all-cause mortality.[162] Similarly, no differences were seen in pooled RCT analyses for fracture outcomes, diabetes incidence, and cardiovascular events. The updated evidence review concluded that "the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults." The authors also highlighted the need for more research regarding the best measures and cut points for vitamin D deficiency, and whether these differ by race, ethnicity, or sex.

A 2014 update of the previously published AHRQ report included 154 newly identified primary studies and two systematic reviews which included an additional 93 primary studies.[27] The group concluded that the, "majority of the findings concerning vitamin D, alone or in combination with calcium, on the health outcomes of interest were inconsistent. Associations observed in prospective cohort and nested case-control studies were inconsistent, or when consistent, were rarely supported by the results of randomized controlled trials." New studies indicate that despite the increase in vitamin D testing, improvements in vitamin D deficiency have not been observed.[7, 8, 163-165]

The IOM report indicated that the current evidence regarding vitamin D intake has not translated into improved patient well-being for conditions not related to bone health.[7] In addition, the IOM committee concluded that, "higher levels have not been shown to confer greater benefits, and in fact, they have been linked to other health problems, challenging the concept that 'more is better.'"[7]

The WTA TEC evidence report was specifically commissioned to evaluate the evidence related to the impact of vitamin D testing and screening on health outcomes.[9] Overall, the report determined, "No definitive conclusions can be drawn about the effectiveness of vitamin D screening or testing since no trials have been conducted to directly assess the impact of screening or testing on health outcomes, patient behavior, or clinical decision making." With the exclusion of populations with known or highly suspected osteoporosis, the WTA report concluded, "…the available evidence suggested no benefit from vitamin D screening (low quality evidence) or was insufficient to permit conclusions."[9]

In addition, the WTA TEC report indicated a lack of evidence demonstrating the effectiveness of supplementation in younger populations, pregnant or lactating women, and subgroups defined by ethnicity and race.[9, 164, 166]

Lack of evidence demonstrating the effectiveness of supplementation according to baseline serum 25(OH)D levels.[9, 10]

The AHRQ report indicated that there is uncertainty regarding how much vitamin D is needed to maintain bone health and normal calcium metabolism in healthy people. The report noted that the optimal level of circulating 25(OH)D required for bone health may also vary depending on the functional outcome.[6] The AHRQ report identified the need for further research to better understand these modifiers of vitamin D effect.

The IOM report does not specify any conditions, including in healthy populations, for which

testing of 25(OH)D serum levels may be indicated.

The reviewed studies of these conditions provided mixed and inconclusive results. Consequently, it cannot be reliably determined whether or how vitamin D affects the risks associated with these conditions, or whether changing the exposure to vitamin D provides a protective effect.

Autier (2017) conducted a systematic review of meta-analyses of vitamin D supplementation and non-skeletal disorders.[167] Publications were included from January 2013 to May 2017, with participants of all ages, including pregnant women. The authors focused on newly published studies in order to elucidate whether the newer RCTs have upheld the historical conclusions of previous RCTs (which did not confirm that vitamin D supplementation could protect from non-skeletal health conditions affecting adults). Studies were selected based on a systematic search, and additional searching for RCTs not included in the meta-analyses. The authors found no new evidence that vitamin D supplementation could have an effect on most non-skeletal conditions, including cardiovascular disease, adiposity, glucose metabolism, mood disorders, muscular function, tuberculosis, and colorectal adenomas, or on maternal and perinatal conditions.

RANDOMIZED CONTROLLED TRIALS

There were no additional RCTs identified which evaluated vitamin D impacts on mortality in healthy populations.

PRACTICE GUIDELINE SUMMARY

ENDOCRINE SOCIETY

The 2024 Endocrine Society updated guideline on vitamin D for the prevention of disease included the following recommendations, all with very low certainty of evidence:[168]

- In the general adult population younger than age 50 years, we suggest against routine 25(OH)D testing.
- In the general population aged 50 to 74 years, we suggest against routine 25(OH)D testing.
- In the general population aged 75 years and older, we suggest against routine testing for 25(OH)D levels.
- During pregnancy, we suggest against routine 25(OH)D testing.
- In healthy adults, we suggest against routine screening for 25(OH)D levels.
- In adults with dark complexion, we suggest against routine screening for 25(OH)D levels.
- In adults with obesity, we suggest against routine screening for 25(OH)D levels.

The guidelines included the following explanatory notes:

- The Guideline Development Panel did not find clinical trial evidence that would support establishing distinct 25(OH)D thresholds tied to outcome-specific benefits in the populations examined. Hence, the Endocrine Society no longer endorses the target 25(OH)D level of 30 ng/mL (75 nmol/L) suggested in the previous guideline. Similarly,

the Endocrine Society no longer endorses specific 25(OH)D levels to define vitamin D sufficiency, insufficiency, and deficiency.

- The current guideline suggests against routine 25(OH)D screening (in the absence of well-established indications), including in adults and children with obesity, in adults and children with dark complexion, and during pregnancy. This also represents a change from the 2011 guideline.

U.S. PREVENTIVE SERVICE TASK FORCE

In 2018, the United States (U.S.) Preventative Service Task Force (USPSTF) concluded that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in men and premenopausal women.[153] The USPSTF also concluded that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. Additionally, the USPSTF recommended against daily supplementation with 400 IU or less of vitamin D and 1000 mg or less of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women. (D recommendation)

Community-dwelling is defined as not living in a nursing home or other institutional care setting. The USPSTF recommendations do not apply to those with a history of osteoporotic fractures, increased risk for falls, or diagnosis of osteoporosis or vitamin D deficiency.

I statements are defined as follows:

> The USPSTF concludes that the current evidence is insufficient to assess the balance and benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

D recommendations are defined as follows:

> The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

The USPSTF guidelines for preventive care are an authoritative standard and are recognized as such by the Affordable Care Act. The USPSTF guidelines do not recommend vitamin D testing for screening purposes. In their 2014 recommendations regarding screening for vitamin D deficiency in adults, the USPSTF concluded that “the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.”[169] This conclusion was unchanged in the 2021 update of this report.[170]

AMERICAN ACADEMY OF FAMILY PHYSICIANS

The American Academy of Family Physicians (AAFP) Summary of Recommendations for Clinical Preventive Services (July 2017) include statements regarding vitamin D supplementation for numerous populations.[171] Vitamin D screening is not addressed. The AAFP recommendations are based upon the USPSTF guidelines noted above.

AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS

In 2011, ACOG issued the following statement regarding vitamin D supplementation in

pregnant women, which was reaffirmed in 2021:[172]

> "At this time there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency. For pregnant women thought to be at increased risk of vitamin D deficiency, maternal serum 25-OH-D levels can be considered and should be interpreted in the context of the individual clinical circumstance. When vitamin D deficiency is identified during pregnancy, most experts agree that 1,000–2,000 international units per day of vitamin D is safe."

WORLD HEALTH ORGANIZATION

In 2020 the World Health Organization (WHO) published an update to their 2016 recommendations for antenatal care, which focused on vitamin D and stated that, "Oral vitamin D supplementation is not recommended for all pregnant women to improve maternal and perinatal outcomes. (Not recommended)"[173]

SUMMARY

There is research showing that vitamin D plays an essential role in promoting bone growth and maintenance, however, there is considerable uncertainty with respect to the clinical utility of testing, both in healthy, asymptomatic populations and for conditions not directly associated with bone health or deficiencies in vitamin D metabolism. Several studies consistently report a lack of evidence demonstrating how vitamin D testing alters treatment decisions or improves health outcomes. In addition, these reports note a lack of information on the levels of vitamin D that define a deficiency. There are no evidence-based clinical practice guidelines that recommend routine vitamin D testing or screening. Additionally, the United States Preventive Services Task Force guidelines, a nationally recognized standard, do not recommend routine screening as a preventive health measure. Therefore, vitamin D testing is considered not medically necessary in the absence of conditions specifically associated with underlying diseases or conditions associated with vitamin D deficiency, decreased bone density, or defects in vitamin D metabolism.

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CODES

Codes	Number	Description
CPT	0038U	Vitamin D, 25 hydroxy D2 and D3, by LCMS/MS, serum microsample, quantitative
	82306	Vitamin D; 25 hydroxy, includes fraction(s), if performed
	82652	Vitamin D; 1,25 dihydroxy, includes fraction(s), if performed
HCPCS	None	

Appendix I
Conditions Specifically Associated with Vitamin D Deficiency
Blind loop syndrome
Calculus of kidney
Calculus of ureter
Celiac disease
Chronic kidney disease

Appendix I
Conditions Specifically Associated with Vitamin D Deficiency
Chronic liver disease
Crohn’s disease
Cystic fibrosis
Disorder of calcium metabolism
Disorders of phosphorus metabolism
End stage renal disease
Granulomatous disease
HIV/AIDS
Hypercalcemia
Hypercalciuria
Hypervitaminosis D
Hypocalcemia
Hypocalcemia and hypomagnesemia of newborn
Intestinal malabsorption
Long-term (current) use of systemic steroids or aromatase inhibitors
Obstructive jaundice
Osteomalacia
Osteogenesis imperfecta
Osteopenia (ICD-10 codes M85.831-M85.839, M85.851-M85.859, M85.80, M85.88, M85.89, M85.9, and M89.9 only)
Osteoporosis
Osteosclerosis/petrosis
Pancreatic steatorrhea
Pancreatitis
Parathyroid disorders
Protein-calorie malnutrition
Rickets
Ulcerative colitis
Transplant (organ [e.g., heart, lung, kidney. liver], bone marrow, or stem cell)
Vitamin D deficiency when on replacement therapy related to a condition listed above; to monitor the efficacy of treatment

Appendix II
Conditions that may be associated with defects in vitamin D metabolism
Calculus of kidney and ureter
Disorders of calcium metabolism
Familial hypophosphatemia
Fanconi syndrome
Hyperparathyroidism
Hypoparathyroidism
Neonatal hypocalcemia
Nephrolithiasis or hypercalciuria

Appendix II
Conditions that may be associated with defects in vitamin D metabolism
Osteomalacia
Rickets
Sarcoidosis
Unexplained hypercalcemia (suspected granulomatous disease or lymphoma)
Unexplained hypercalciuria (suspected granulomatous disease or lymphoma)

Date of Origin: *February 2011*