Washington State Health Care Authority

Health Technology Assessment

Vitamin D Screening and Testing

Final Evidence Report

November 16, 2012

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126

http://www.hta.hca.wa.gov
SHTAP@HCA.WA.GOV

Vitamin D Screening and Testing

A Health Technology Assessment

Prepared for Washington State Health Care Authority

FINAL REPORT – November 16, 2012

Acknowledgement

This report was prepared by:

Hayes, Inc.
157 S. Broad Street – Suite 200
Lansdale, PA 19446
P: 215.855.0615 F: 215.855.5218

Table of Contents

EXECUTIVE SUMMARY

Background

Vitamin D and Health Disorder

Examples of disorders that have traditionally been understood to be *caused by* vitamin D insufficiency are related to bone health. They include rickets, osteomalacia, and osteoporosis. Vitamin D insufficiency may also affect muscle strength. Therefore, falls as well as fractures may be patient-important results of vitamin D insufficiency. Accumulating evidence suggests that the effects of vitamin D insufficiency are protean, i.e., that they are manifest in multiple organs and systems, not just in musculoskeletal tissue. Vitamin D insufficiency may also be the *result* of a medical condition. Some diseases, notably chronic kidney disease (CKD) and sarcoidosis, can cause vitamin D depletion. Conditions that cause malabsorption can also result in vitamin D deficiency.

Vitamin D Deficiency

Vitamin D stores derive from cutaneous production in response to sun exposure and, to a lesser extent, from dietary sources. Historically recommended daily intakes of vitamin D are often not adequate if sunlight exposure is limited. The wintertime sunlight in regions higher than 35 degrees latitude, which would include the state of Washington and most of the mainland United States, does not include enough ultraviolet B (UVB) radiation to stimulate cutaneous vitamin D production. Furthermore, factors such as the time of day of sunlight exposure, clothing, sunscreen use, pigmentation, and age influence UVB absorption and the effectiveness of sun exposure so that even individuals who live in sunny climates may be at risk of vitamin D insufficiency. (NOTE: The phrase *at risk of vitamin D insufficiency* is used because individuals who have risk factors associated with lower levels of vitamin D do not necessarily have serum levels below a certain cutoff value. The phrase also acknowledges that the same concentration of serum vitamin D may be inadequate in some individuals and adequate in others.) Additional factors that may be associated with lower vitamin D status include breastfeeding in infants, female sex, and obesity.

Data for the years 2001 to 2006 from the periodic National Health and Nutrition Examination Survey (NHANES) revealed that approximately one third (33%) of the U.S. population was at risk of vitamin D *insufficiency*, defined by the Institute of Medicine (IOM) as serum levels of 25-hydroxyvitamin D (25-OHD) below 50 nanomoles per liter (nmol/L) (20 nanograms per milliliter [ng/mL]). The NHANES report did not provide vitamin D insufficiency data by state and no data specific to the general population of Washington State were identified in the published literature. Many laboratories that offer vitamin D testing use cutoff values that are much higher than the 50 nmol/L or 20 ng/mL recommended by the IOM.

Rationale for Testing, Monitoring, and Screening

Several *clinical factors* suggest the potential for vitamin D insufficienty or deficiency and thus may be indicators for vitamin D *testing*. Relevant conditions include poor nutrition, malabsorption due to gastrointestinal disease or malabsorptive bariatric surgery, hepatic dysfunction, and renal dysfunction or age-related renal changes. Laboratory findings that suggest possible vitamin D deficiency include low urine calcium excretion, elevated parathyroid hormone level, elevated alkaline phosphatase, lower

serum calcium, and low serum phosphorous. Radiographic findings that might raise suspicion of deficiency include osteopenia/osteoporosis, nontraumatic fracture, and skeletal pseudofracture.

In the absence of clinical indicators, vitamin D testing would be considered *screening*. The purpose of screening would be to assess the need to improve vitamin D status as a preventive measure against health problems. Screening in healthy populations could be universal (routine), or it could be based on demographic or lifestyle factors that are associated with low serum vitamin D (high risk). Screening in populations defined by the presence of diseases such as cancer or diabetes would be for the purpose of assessing the need to improve vitamin D status as a way of improving disease-related outcomes. Vitamin D screening is more controversial than vitamin D testing.

Treatment of Insufficiency, Recommended Intake, and Toxicity

Vitamin D insufficiency can be treated by sunlight, artificial UVB light, changes in diet, and vitamin D supplementation. The IOM's Dietary Reference Intake (DRI) values for vitamin D intake in generally healthy populations are designed to serve the needs of almost all (97.5%) individuals, regardless of sun exposure. The IOM currently recommends a daily intake of 600 international units (IU) in adults and children, 400 IU in infants, and 800 IU in adults > 70 years of age. According to systematic reviews conducted for the Agency for Healthcare Research and Quality (AHRQ), serum 25-OHD levels rise with increased dietary intake of vitamin D from fortified foods and with vitamin D supplementation with or without calcium.

The harms associated with vitamin D toxicity include kidney and other tissue damage and kidney stones. The daily upper level intake (UL) values set by the IOM are 1000 IU per day for infants ≤ 6 months, 1500 IU/day for infants 6 to 12 months, 2500 IU/day for children aged 1 to 3 years, 3000 IU/day for children ages 4 to 8 years, and 4000 IU/day for children > 8 years and for adults. Available data defined 10,000 IU/day as the maximum dose corresponding to a no observed adverse event level (NOAEL). However, the UL was set considerably lower than 10,000 IU because of the lack of data on long-term adverse events associated with very high doses of vitamin D.

Measurements Involved in Testing and Monitoring

Since all ingested and cutaneously produced vitamin D is converted to 25-OHD, measuring and properly interpreting the circulating 25-OHD concentrations is the generally accepted measure of vitamin D status. A recent IOM committee concluded that serum levels ≥ 30 to 50 nmol/L were sufficient for maximum skeletal calcium absorption in children and adults, regardless of sun exposure. (The committee did not make recommendations concerning screening or testing.)

Technology Description

Serum 25-hydroxyvitamin D (25-OHD) assays fall into three general categories: competitive protein binding (CPB) assays, immunoassays, and chromatographic assays. Chromatographic methods include high performance liquid chromatography (HPLC) and liquid chromatography with mass spectrometry or tandem mass spectrometry (LC-MS or LC-MS/MS). There are commercially available kits, some of them with Food and Drug Administration (FDA) approval, within each category, but chromatography-based assays typically use "home-brew" processes. Different assay types produce discordant results when applied to the same human serum. An assessment of the accuracy of assays is hampered by the lack of a true reference standard. Currently, authors refer to either the HPLC or the LC-MS/MS as the "gold

standard." However, chromatography, as well as CPB methods, are time consuming and expensive; thus, manufacturers have developed immunoassays as cheaper alternatives. In the absence of a universal reference standard for in-house calibration, it is possible for clinical laboratories offering vitamin D testing services to assure good-quality performance by participating in an External Quality Assessment Scheme (EQAS).

Key Questions

1. Has a relationship between serum vitamin D and health outcomes been demonstrated and have clinically valid cutoff points for serum vitamin D measurement been defined (*clinical validity*)?

    a. In healthy populations?
    b. In patients with chronic disease?

2. Is there evidence that testing for serum vitamin D levels improves health outcomes (*clinical utility*)?

    a. As a routine screening test in healthy patients?
    b. In patients who already have chronic disease thought to be associated with low serum vitamin D?

3. Are there harms associated with vitamin D testing or with subsequent supplementation?

4. What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in (a) healthy populations and (b) populations who already have chronic disease, according to factors such as:

    <u>Patient characteristics</u>

    i. Age or life stage
    ii. Race or ethnicity
    iii. Geographic location
    iv. Nutritional status, diet, or personal use of calcium/vitamin D supplements
    v. Lifestyle factors such as smoking
    vi. Obesity
    vii. Baseline serum vitamin D level
    viii. Baseline risk of the health outcome of interest

    <u>Testing parameters</u>

    ix. Assay used
    x. Frequency of monitoring
    xi. Time of year

5. What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?

NOTE: *Healthy*, as used here, refers to absence of a disease known to cause vitamin D insufficiency, such as chronic kidney disease (CKD), and absence of the types of chronic disease for which vitamin D has been thought to create a risk. Study populations that were unselected on the basis of disease were considered healthy populations.

Methods

Search Strategies

There is a very large volume of clinical literature on vitamin D and a number of ways in which vitamin D status may be related to health outcomes. We focused our analysis on Key Questions #2 through #4, which relate to the clinical utility of vitamin D screening and testing. For Key Question #1, which relates to the clinical validity of test results, representative evidence was summarized in a descriptive manner. For Key Questions #2 through #4, several systematic attempts were made to identify clinical trials designed to measure the direct effect of vitamin D screening/testing on patient outcomes and the effect of screening/testing on increased intake through changes in patient behavior or clinical management decisions. These searches failed to identify any studies. Nor was this type of evidence discussed in recent systematic reviews, narrative review articles, or practice guidelines. Therefore, the Washington HTA Program chose to assess the impact of increased intake (supplementation) on patient outcomes as an indicator of the *potential* utility of screening/testing. *Screening or testing would not improve health outcomes if there were no effective treatment that could be recommended for individuals with low serum vitamin D.* Evidence considered for Key Question #2 addresses the issue of whether supplementation is an effective treatment and potentially identifies populations in which screening or testing might be effective. Evidence considered for Key Question #4 comes from the same trials selected for Key Question #2 but addresses the issue of whether the effectiveness of supplementation varies according to patient characteristics. If supplementation is only effective in individuals who are at high risk of vitamin D insufficiency because of factors such as age or race or who have high baseline risk of the outcome of interest, such findings would further define the subpopulations in which screening or testing might be effective. If the effect of supplementation differs according to baseline serum levels, then there is a clinical reason to test serum levels to assess the need for supplementation. We took a pragmatic approach to searching for and selecting systematic reviews and randomized controlled trials (RCTs) to answer Key Questions #2 through #4.

The National Health Service Economic Evaluation Database (NHSEED) and MEDLINE were searched for economic evaluations. Practice guidelines were identified through searches of MEDLINE, systematic review databases, the National Guidelines Clearinghouse, and relevant professional associations.

Quality Assessment

Hayes' usual quality methods were used for assessing the quality of primary studies and bodies of evidence (see Appendix II). Internally developed Quality Checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *Good, Fair, Poor, or Very Poor*. The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account not only methodological quality in individual studies but also the applicability of bodies of evidence to the population(s), intervention(s), and health outcome(s) of interest; the consistency of results across studies; and the quantity of data (number of studies and sample sizes). The quality of bodies of evidence for particular outcomes are labeled as *High, Moderate, Low, or Very Low*. Overall bodies of evidence are assessed according to the quality of the lowest-quality body of evidence for a key outcome. The Appraisal of Guidelines Research and Evaluation (AGREE) (AGREE Enterprise, 2012) tool was used to assess the quality of practice guidelines.

Search Results

Overall results can be summarized as follows:

Key Question #1: 13 systematic reviews, 6 narrative reviews, 3 observational studies.

Key Questions #2 to #4: 10 systematic reviews, 41 randomized controlled trials (RCTs) or trial reports.

Key Question #5: 1 cost analysis, 3 cost-effectiveness studies.

Practice Guidelines and Public Health Policies: 26 documents reviewed, of which 17 had recommendations pertinent to this report.

Findings

Key Question #1a: Has a relationship between serum vitamin D and health outcomes been demonstrated *in healthy populations* and have clinically valid cutoff points for serum measurement been defined (clinical validity)?

A noncritical review of recent systematic reviews, narrative reviews, and clinical trials supports the following description of what is known about the link between serum levels of vitamin D and the risk of disease.

Evidence identified in recent systematic reviews suggests that serum 25-OHD levels have a *harmful association with overall cancer mortality* (men only). In other words, high serum levels are associated with increased cancer mortality in men.

Systematic reviews have shown that higher serum 25-OHD levels have a *protective association with bone health*. Fair-quality (according to the systematic reviews) evidence has shown a link with bone mineral density (BMD) in some populations, but evidence to date has not demonstrated an association with health outcomes such as fractures or falls, and recent systematic reviews suggest that no studies have investigated a link with any measure of bone health in younger adults. The evidence identified in recent systematic reviews also suggests that higher levels of serum 25-OHD may *protect* adults against *cardiovascular disease (CVD), type 2 diabetes, colorectal cancer, ovarian cancer, and all-cause mortality*.

There is an *unclear association* of vitamin D with risk of *cancer other than colorectal cancer or ovarian cancer*. The results as reported in the literature reviewed for this report were inconsistent.

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. The selected literature also did not provide data specific to *pediatric populations*.

Cutoff Values

For disease outcomes where a link has been demonstrated, the evidence does not support clinically valid definitive cutoff points at which 25-OHD serum levels can be expected to predict optimal overall

health. Some studies have conducted analyses according to different strata of serum levels and studies have varied as to how those strata are defined. Other studies have analyzed associations treating serum level as a continuous variable without specifying a cutoff value. Furthermore, optimal thresholds may vary by the outcome of interest. However, evidence to date is consistent with approximately 30 nmol/L as the level below which there is a risk of deficiency and a threshold ≥ 50 nmol/L, and possibly as high as 70 nmol/L, for optimal health.

Implications for Vitamin D Screening

Screening for low vitamin D levels in healthy populations could serve to provide a general health indicator, given the association with several forms of chronic disease and with all-cause mortality. However, the lack of definitive cutoff points diminishes the validity of serum measurements and thereby sheds doubt on the utility of vitamin D screening, and findings of a possible harmful association between serum 25-OHD and cancer mortality in men complicates interpretation of serum measurements.

Key Question #1b: Has a relationship between serum vitamin D and health outcomes been demonstrated in populations with *chronic disease* and have clinically validated cutoff values for detection of vitamin D deficiency been defined (clinical validity)?

In the literature reviewed for this report, there was very sparse evidence concerning an association between serum levels of 25-OHD and disease-related outcomes in individuals with chronic disease. A very small quantity of data suggests that higher levels of serum 25-OHD may be associated with better prognosis for some types of cancer (colon, prostate, and melanoma; longitudinal data), fewer cardiovascular events in individuals with hypertension (longitudinal data), fewer complications in individuals with diabetes (longitudinal and cross-sectional data), fewer relapses in individuals with MS (cross-sectional data), and less severe symptoms in individuals with depression (cross-sectional data). Cutoff points have not been established. Cross-sectional data do not shed light on the direction of causality. The literature reviewed did not provide data on pediatric populations defined by disease presence.

Implications for Vitamin D Screening

Vitamin D screening may have promise for establishing a prognosis in patients with colon cancer, prostate cancer, or melanoma and for assessing the risk of disease-related events and complications in patients with hypertension and diabetes. However, the evidence is too sparse to support clinical rules or cutoff points.

Key Question #2a: Is there evidence that testing for serum vitamin D levels as a routine screening test in *healthy* populations improves health outcomes (clinical utility)?

As noted in the **Methods** summary, the literature does not provide direct evidence of the effectiveness of vitamin D screening. Six systematic reviews and 14 RCTs (23 publications) evaluating the effect of vitamin D supplementation on the health outcomes of interest were identified. It is noteworthy that study participants were not selected on the basis of vitamin D test results.

One of the selected RCTs was the Women's Health Initiative (WHI), a 7-year study following 36,282 postmenopausal women. Women were randomized to 400 IU/day of vitamin D plus calcium, or to placebo, and were allowed continued use of personal supplements. Baseline serum 25-OHD levels were

not reported for the overall study group. However, a nested case-control analysis derived from this study, as well as national surveys, show that a substantial proportion of postmenopausal women have vitamin D insufficiency (serum levels < 50 nmol/L), but the prevalence of vitamin D insufficiency in the WHI trial was considerably greater than what national surveys have indicated for the national population of women in this age group. Nine different publications provided data from this trial that were pertinent to Key Question #2a.

The evidence suggests *a benefit from supplementation* (low-quality evidence) for these outcomes and populations:

- *Musculoskeletal health in older adults*, especially when combined with calcium: improved BMD (9 RCTs), reduced risk of falls (1 meta-analysis of 26 RCTs; 46,782 participants); reduced risk of fracture if vitamin D is combined with calcium (1 meta-analysis of 11 RCTs; 52,915 participants). Participants were predominantly postmenopausal women.
- *Reduction of mortality in older adults* (2 RCTs; 38,968 participants, predominantly postmenopausal women). The findings are consistent with a systematic review of studies involving adults (all ages) with and without baseline disease.

The evidence suggests *no benefit from supplementation* (low- to moderate-quality evidence) for these outcomes and populations:

- *Prevention of diabetes in adults* (2 RCTs; 33,951 postmenopausal women and 342 middle-aged adults) (low quality).
- *Prevention of mood disorders in adults* (3 RCTs, 4625 participants) (moderate quality).

There is an *uncertain benefit from supplementation* (low-quality evidence primarily because of inconsistency in study results) for these outcomes and populations:

- *Bone health in infants, children, and adolescents:* Bone mineral content (BMC) and BMD (cumulative evidence in 3 systematic reviews).
- *Prevention of obesity in adults* (3 RCTs; 36,687 participants).
- *Prevention of cancer in older adults* (may vary by cancer type) (3 RCTs; 40,165 participants, predominantly postmenopausal women).
- *Prevention of cardiovascular disease in older adults* (2 RCTs; 38,968 participants, predominantly postmenopausal women).
- *Promotion of greater birth size and weight through maternal supplementation in late pregnancy* (3 RCTs; 422 participants).

There is *insufficient evidence regarding a benefit from supplementation* (no evidence or single small trials) for these outcomes and populations:

- *Prevention of multiple sclerosis (MS).*
- *Improvement of nonskeletal health outcomes* in *younger adults, lactating women, infants, children, and adolescents.*

Quality and Relevance of the Evidence Regarding Supplementation

Evidence for each general outcome is of low quality with respect to the benefit of supplementation (one exception: moderate-quality evidence regarding prevention of mood disorders). Common weaknesses included estimates of relative risk that favored vitamin D but were statistically nonsignificant; variable vitamin D doses across studies, with studies using low doses more likely to report negative or nonsignificant results; and varied protocols with respect to the use of nonstudy vitamin D. There was a dearth of evidence pertaining to younger populations. Where the evidence suggested a benefit, the effects were small.

Implications for Vitamin D Screening

Given the evidence suggesting positive effects of supplementation on *musculoskeletal health* and general *mortality* in older adults, screening for low vitamin D status might be effective for these particular outcomes, but that would depend on whether effects vary according to baseline serum levels. Evidence to date regarding the effectiveness of increased vitamin D intake through supplementation does not in general support vitamin D screening to improve *nonskeletal* health outcomes other than mortality. However, an analysis of differential effectiveness by patient risk factors and baseline serum levels could modify this conclusion. See Findings for Key Question #4a.

Key Question #2b: Is there evidence that testing for serum vitamin D levels as a routine screening test in patients with chronic disease improves health outcomes (clinical utility)?

As noted in the **Methods** summary, the literature does not provide direct evidence of the effectiveness of vitamin D screening. Three systematic reviews and 16 RCTs (18 publications) evaluating the effect of vitamin D supplementation on disease-related outcomes in the populations of interest were identified. Study participants were not selected on the basis of vitamin D test results.

The evidence suggests a *benefit from supplementation* for these indications (moderate-quality evidence):

> Improvement of bone health in *patients with osteoporosis or history of fracture using active forms of vitamin D* (15 RCTs).
> Improvement of disease-related outcomes in patients with *cardiovascular disease* (8 RCTs).
> Improvement of disease-related outcomes in patients with *abnormal blood glucose* (type 2 diabetes, impaired glucose tolerance, or insulin resistance) (12 RCTs).

The evidence suggests *no benefit from supplementation* for these indications (moderate-quality evidence):

> Bone health in *patients with osteoporosis or history of fracture using inactive vitamin D* (4 RCTs).
> Weight-related and cardiometabolic outcomes in *obese adults* (5 RCTs; moderate-quality evidence).

There is an *uncertain benefit* from supplementation for these indications (low-quality evidence because of inconsistency in direction of study results or inconclusive pooled estimates):

> Survival in patients with *advanced prostate cancer* (3 RCTs)
> Disease-related outcomes in patients with *MS* (4 RCTs)

There was *insufficient evidence* (no evidence or single small RCTs) for these indications:

Patients with *cancer other than prostate cancer*
Individuals with *depression or another mood disorder*
All-cause mortality in any population

Quality and Relevance of the Evidence Regarding Supplementation

Evidence ranged from low to moderate quality, depending on the disease population. It should be noted that even in the disease populations where the evidence showed a benefit, *the effects were small and may not be clinically relevant* (an exception was the effects of active vitamin D supplementation on bone health in older adults with osteoporosis or a history of fracture).

Implications for Vitamin D Testing or Screening

Given the evidence of the effectiveness of active forms of vitamin D, vitamin D testing in patients who have evidence of osteoporosis has the potential to improve bone-related outcomes. Given the evidence showing supplementation to modestly improve disease-related outcomes in individuals with cardiovascular disease or abnormal blood glucose, vitamin D screening to assess the risk of adverse disease outcomes might be effective in these populations. However, a conclusion that testing or screening is effective in these clinical situations depends on whether the effectiveness of supplementation varies according to baseline serum levels. Evidence to date regarding the effectiveness of increased vitamin D intake through supplementation does not in general support screening in other disease populations. However, an analysis of differential effectiveness by patient risk factors and baseline serum levels could modify this conclusion. See Findings for Key Question #4b.

Key Question #3. Are there harms associated with vitamin D testing or with subsequent supplementation?

Vitamin D testing is a safe procedure, and vitamin D therapy is a reasonably safe treatment. Supplementation with inactive vitamin D is associated with a moderate increase in the risk of both hypercalcemia and kidney stones, which are related conditions. Treatment with active (pharmaceutical) vitamin D is associated with an approximately threefold increase in the risk of hypercalcemia. Vitamin D therapy may be associated with musculoskeletal and gastrointestinal symptoms, but a causal relationship has not been proven, and no serious adverse events have been reported in trials of vitamin D supplementation.

Quality of the Evidence

Considering the quantity of data, consistency of results, and the quality of individual studies (as directly assessed and as reported by systematic reviews), the body of evidence concerning the safety of vitamin D is of moderate quality, and the quality of the evidence concerning the safety of active vitamin D is of low quality due to a smaller quantity of data.

Key Question #4a: What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in *healthy* populations?

As previously noted, no trials were found that assessed the effect of vitamin D screening or testing on health outcomes, patient behavior, or clinical decisions. Thus, there is no direct evidence regarding the differential effectiveness and safety of vitamin D screening or testing. The RCTs selected for evidence of the effectiveness of vitamin D supplementation in healthy populations served as evidence of whether the *potential* effectiveness and safety of vitamin D screening might differ according to patient characteristics or testing parameters. The bulk of the evidence is derived from focused analyses of the Women's Health Initiative study, which involved 36,282 postmenopausal women (all older than 50 years of age) who were randomized to vitamin D (400 IU/day) plus calcium and followed for 7 years. As noted in the discussion of findings for Key Question #2a, the prevalence of vitamin D insufficiency was much greater in the WHI trial population (estimated 72% with 25-OHD levels <52.4 nmol/L) than in the general population of American women aged 50 years or older (28% with levels < 50 nmol/L).

The following evidence was available concerning *older adults*:

Metaregression Analysis in Systematic Reviews

- There is a *differential effect of supplementation on falls according to baseline serum levels*, but not among community-dwelling adults (low quality). A systematic review that included studies conducted in all settings detected a substantial difference between data pertaining to subpopulations with known or presumed vitamin D deficiency (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.39 to 0.72) and data pertaining to individuals without evidence of deficiency (OR, 0.90; 95% CI, 0.81 to 0.99). However, for some studies, an assumption of vitamin D deficiency was made only on the basis of risk factors. A systematic review of supplementation in community-dwelling older adults detected no differential effect by baseline levels of serum 25-OHD on falls.
- *Differential effect of supplementation on nonvertebral fractures by baseline serum levels* (low-quality evidence). The most recent systematic review on vitamin D and fractures included a meta-analysis showing a statistically significant protective treatment effect only in individuals with baseline serum 25-OHD levels > 43 nmol/L. . No pooled analysis of differential effect on vertebral fractures was possible.

- *No differential effect of supplementation on falls by sex, age, or other baseline risk factors* (low-quality evidence).

Subgroup or Regression Analyses Within a Trial

- *Generally, no differential effect of supplementation, or unclear effect, on numerous outcomes in postmenopausal women* (low-quality evidence).Numerous analyses of a single, very large, good-quality trial with 7-year follow-up detected no differential effect of vitamin D supplementation on risk of fracture, weight control, risk of various forms of cancer or CVD and related mortality, risk of diabetes, or all-cause mortality. Data were available pertaining to the interaction of treatment with all of the patient-related factors of interest specified in the Key Question. There was some suggestion of a differential effect according to baseline serum levels of 25-OHD for colorectal cancer (CRC), hypertension, and all-cause mortality, but the direction of trends was contradictory across outcomes and no statistically significant stratum-specific effects were detected. A single small RCT also found no differential effect on mental health measures according to baseline serum 25-OHD.

- *Exception:* Positive effects on risk of fracture in postmenopausal women only in those with a history of ≥ 3 fractures (very–low-quality evidence).

The following evidence was available on c*hildren and adolescents* (metaregression analyses in systematic reviews; low-quality evidence):

- *Uncertain differential effect of supplementation on BMD by baseline serum levels.*
- *No differential effect of supplementation on BMD by age.*

There was *insufficient evidence* regarding the following factors, populations, and outcomes:

- *Differential safety of supplementation for any population*.
- *Differential effectiveness according to testing parameters for any population.*
- *Differential effectiveness according to any factor in younger adults*, *pregnant women*, *or lactating women.*
- *Differential effectiveness for prevention of obesity*, *multiple sclerosis (MS)*, *or depression and mood disorders.*

Quality and Relevance of the Available Evidence Regarding Supplementation

The conflicting evidence regarding a differential effect on falls in older adults according to vitamin D status may be explained by more frail study participants in the review with positive results, as well as the authors' assumption that populations with ≥ 2 risk factors for low serum 25-OHD actually were vitamin D deficient. The seemingly contradictory findings of greater reduction in falls in vitamin D-*deficient i*ndividuals but greater reduction in fractures in vitamin D-*sufficient* individuals are difficult to reconcile. The data on subgroup effects on musculoskeletal health were derived from metaregression analysis, which is subject to ecological bias (Murad et al., 2011). In other words, observed relationships between the studies characterized by a mean value for a particular patient factor and the studies reporting a particular treatment effect, does not necessarily mean that the relationship exists in individuals. The results are heavily influenced by the very large WHI trial, from which a case-control sample indicated a much larger than typical proportion of women with vitamin D insufficiency at baseline. It is possible that the differential effects of supplementation on some outcomes might be detected in large populations representing a wider range of vitamin D status. Evidence pertaining to nonskeletal outcomes came from a single trial, which was a generally good-quality trial, but the follow-up interval might not have been sufficiently long to capture differential effects on mortality or some forms of cancer. Other trials corroborating the results from this trial have not been published. Furthermore, all of the trial participants were postmenopausal women; the results might not be generalizable to men or younger adults. The overall body of evidence concerning a differential effect by patient characteristics is of low quality.

Implications for Vitamin D Screening

Musculoskeletal Benefits: Evidence pertaining to differential effects does not support a clear role for vitamin D screening to improve musculoskeletal outcomes. Supplementation in older adults has been shown to be helpful for preventing falls, especially in subpopulations with known or suspected vitamin D deficiency, but the evidence does not permit a distinction between the effect of supplementation in older adults with risk factors for vitamin D deficiency and the effect in older adults who have known

deficiency based on serum measurements. Other evidence showing that supplementation is effective in community-dwelling older adults, but that effectiveness does not vary according to baseline serum levels in this subpopulation, suggests that screening would not have utility in community-dwelling older adults. There is some evidence that in an overall population of older adults (institutionalized and community-dwelling), the effectiveness of supplementation on falls and fractures varies by baseline vitamin D status, but the trends are in opposite directions for the two outcomes. Other patient characteristics do not appear to be helpful in identifying subpopulations of older adults likely to have the greatest benefit from increased intake; thus, patient factors other than serum levels are not helpful in selecting older adults for screening. For adolescents and children, the evidence to date does not suggest that the musculoskeletal benefits of increased intake are dependent on baseline serum levels, and thus the utility of vitamin D screening is questionable in these populations.

Nonskeletal Benefits: Evidence to date applies only to postmenopausal women, is derived from a single trial, and has not proven differential nonskeletal benefits according to baseline serum 25-OHD levels or any other patient characteristics. There was some very–low-quality evidence suggesting variable effects across different strata of baseline serum 25-OHD, but trends for different outcomes were contradictory. Thus, vitamin D screening in postmenopausal women would have to be outcome-specific and the utility of screening in other populations is unknown.

Key Question #4b: What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in patients who *already have chronic disease*?

NOTE: Although the key question refers to *testing*, *screening* is a more appropriate term since the implied target populations are generally unselected, i.e., *not* identified on the basis of signs or symptoms of vitamin D insufficiency. The exception is vitamin D and known or suspected osteoporosis.

The RCTs and systematic reviews selected for evidence of the effectiveness of vitamin D supplementation and potential utility of vitamin D screening/testing in populations with chronic disease were reviewed for evidence of differential effectiveness and safety. None of the selected systematic reviews discussed effectiveness by patient factors.

The evidence suggested *no differential effect of supplementation on glycemic control in adults at high glycemic risk according to baseline serum 25-OHD* (low-quality evidence). Analyses in 1 trial evaluating the effect on the oral glucose tolerance test in obese women and the pattern of results in 11 trials evaluating the effect on glycemic control in adults with abnormal glucose control suggested no differential effects according to baseline serum 25-OHD.

There was *insufficient evidence of the effect of supplementation on other outcomes or according to other factors*. There was no evidence pertaining to the differential effectiveness of vitamin D supplementation with regard to sex, ethnicity/race, geographic location, lifestyle factors, or baseline disease-related risk. There were data from single small trials pertaining to effectiveness according to age, baseline obesity (nonsignificant interaction), and baseline intake of calcium (significantly positive for interaction). No trials addressed the issue of differential safety, and there was no evidence pertaining to differential effectiveness according to testing parameters.

Implications for Vitamin D Screening

Overall, the evidence is insufficient to allow conclusions about either the differential effectiveness and safety of supplementation or the potential utility of vitamin D screening/testing according to patient and testing factors for most outcomes, but low-quality evidence suggesting no differential effect on glycemic control according to baseline serum levels of 25-OHD suggests that vitamin D screening would not have utility for assessing the need to address this particular outcome with supplementation.

Key Question #5: What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?

A single vitamin D test could cost a payer or a consumer more than supplementation for a year with over-the-counter vitamin D2 or D3 at doses recommended by the IOM and, depending on the duration of therapy. Testing with follow-up monitoring might likewise exceed the cost of supplementation with active (pharmaceutical) vitamin D. There is evidence from three cost-effectiveness studies in Canada and Europe that routine supplementation with vitamin D3 in postmenopausal or institutionalized women can reduce lifetime costs associates with hip fracture or the cost of treating hip fractures.

Quality and Relevance of the Evidence

The cost-effectiveness studies were generally well designed. The evidence was considered to be of moderate quality for the limited indication that was addressed. However, the selected studies did not consider vitamin D testing to be one of the costs associated with supplementation. Furthermore, since no trials have assessed the effectiveness of vitamin D testing itself, a cost-effectiveness analysis of vitamin D testing is not possible.

Implications for Vitamin D Screening

Consistent evidence suggesting that routine supplementation in older populations reduces the costs associated with hip fracture also suggests that there is no need for vitamin D screening to identify subpopulations in whom there is a potential for such cost savings. For other populations and outcomes, there is no evidence pertaining to the cost implications of vitamin D testing or screening.

Practice Guidelines and Public Health Policies

Seventeen generally good-quality guidelines addressed vitamin D testing and/or supplementation in populations relevant to this report. The guidelines' recommendations for supplementation are consistent with current IOM recommendations.

Three good-quality guidelines, one fair-quality guideline, and one very–poor-quality guideline recommend against routine screening for vitamin D status: in adults and children (The Endocrine Society; Medical Advisory Secretariat (MAS), Ontario; Osteoporosis Canada), in pregnant women (ACOG), and in children (AAP). The Endocrine Society, MAS, and ACOG guidelines also explicitly or implicitly support screening in individuals who are at general high risk, but definitions of high risk are lacking. The guidelines identify general factors such as sun exposure, dark skin, and nutritional intake as risk factors in their background sections. Osteoporosis Canada recommends testing and supplementation in individuals being treated pharmaceutically for osteoporosis and follow-up testing at 3 to 4 months.

These recommendations against routine screening are consistent with the lack of direct evidence that vitamin D testing improves outcomes, as well as the general lack of moderate or high-quality evidence that supplementation improves outcomes in healthy populations. The at-risk populations that the guidelines imply might be appropriate for routine screening are defined in part by demographic and lifestyle factors that have a known association with lower serum levels. However, there is no evidence demonstrating that screening or supplementation in groups defined by these factors is more effective than in the general population.

Three fair- to good-quality guidelines recommend testing in populations with known poor bone health: children with skeletal fragility (AAP) and adults with osteoporosis (Institute for Clinical Systems improvement [ICSI], Osteoporosis Canada). These recommendations are weakly supported by evidence of the effectiveness of supplementation in these populations, but there is no direct evidence concerning the clinical utility of testing. The Osteoporosis Canada guidelines add that monitoring is not necessary at vitamin D doses < 2000 IU/day because such doses are safe but that monitoring every 3 to 4 months until adequate levels are achieved is advised for patients undergoing pharmacologic therapy. Two good-quality guidelines by the National Institute for Health and Clinical Excellence (NICE) on pharmaceutical treatments for primary and secondary prevention of osteoporosis assume that women are vitamin D replete. However, the NICE guidelines do not offer guidance on recommended intake, supplementation, or testing.

Other guidelines recommending vitamin D testing only addressed indications that are outside the defined scope of this report: CKD, use of obesity medications that cause vitamin D depletion, and history of malabsorptive bariatric surgery. These guidelines were not evaluated for quality.

Selected Payer Policies

Neither the Centers for Medicare & Medicaid Services (CMS) nor GroupHealth has a policy regarding vitamin D testing or vitamin D supplementation. Aetna covers injections of two forms of active vitamin D calcitriol and paricalcitol) for treatment of hypocalcemia and/or secondary hyperparathyroidism, but only in individuals undergoing hemodialysis for chronic renal failure. Regence Group covers serum 25-OHD and 1,25-(OH)2-D testing in individuals who either have a documented disease or condition known to cause vitamin D depletion, e.g., metabolic disorders, or have radiologic or laboratory findings that are positive for markers for insufficiency, e.g., osteoporosis or hyperparathyroidism. Except for osteoporosis and rickets, conditions covered by Regence Group for vitamin D testing are not among the indications of interest that were specified in the PICO (Population/Intervention/Comparator/Outcome) statement for this evidence report.

Overall Summary and Discussion

Evidence-Based Conclusions

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. However, for some populations and outcomes, an association between serum levels and health outcomes and/or a positive effect of supplementation on health outcomes has been demonstrated. Thus, vitamin D screening has *potential* utility for identifying individuals who could benefit from the preventive or disease-modifying effects of supplementation in

these clinical situations. Both vitamin D screening/testing and vitamin D supplementation are generally safe interventions.

There are two areas where information about vitamin D serum levels might have value:

(a) To demonstrate the need for supplementation as a means of reducing disease and mortality risk in postmenopausal women (overall, very low quality evidence). Our confidence in this conclusion is very weak. This conclusion reflects these findings:

- Evidence of an association between serum 25-OHD and all-cause mortality, some forms of cancer, and cardiovascular disease in adults, but lack of a definitive cutoff value for serum 25-OHD.
- Low-quality evidence that supplementation prolongs survival and improves outcomes related to some forms of cancer and cardiovascular disease in older adults.
- Low-quality evidence that in postmenopausal women the effectiveness of supplementation for these outcomes varies by baseline serum levels of 25-OHD (but the direction of trend is different for different outcomes).
- Unknown cost-effectiveness of supplementation without prior assessment of vitamin D serum levels for these particular outcomes.

(b) To inform treatment for individuals with known or highly suspected osteoporosis (overall, moderate-quality evidence). We can have reasonable confidence that the available evidence represents the true value of vitamin D testing for this indication. This conclusion is based on these considerations:

- Evidence of an association between serum levels and musculoskeletal health in patients with osteoporosis.
- Moderate-quality evidence of the effectiveness of supplementation with active vitamin D for improving bone health in individuals with osteoporosis or high suspicsion of osteoporosis.
- Recognition of osteoporosis as an objective marker for insufficient serum vitamin D levels.
- Common use of active (pharmaceutical) forms of vitamin D in patients with osteoporosis, as suggested by published trials. Active forms are more likely than inactive vitamin D to produce toxicity. Treatment of osteoporosis could also conceivably involve *inactive* vitamin D at doses higher than those considered by the IOM to be safe for routine use (4000 IU/day), thus requiring monitoring both to avoid vitamin D toxicity during treatment and to determine when high-dose supplementation can be discontinued.

An additional indication for vitamin D screening might be considered reasonable based on the available evidence. That would be screening to assess the need for supplementation to promote musculoskeletal health in adult populations selected only because of older age. There is an association between vitamin D status and BMD in this population, as well as a positive effect of vitamin D supplementation on BMD, falls, and fractures. Whether the overall effect on musculoskeletal health differs by baseline vitamin D status is unclear; findings to date are difficult to reconcile. At any rate, since routine supplementation of postmenopausal or institutionalized women *without screening* has been shown to be cost-effective as a

preventive treatment for fracture, screening would seem to be an unneeded expense in older women. Since the effect of supplementation was found not to vary by sex, the cost-effectiveness of routine supplementation without screening in men might also be inferred.

For other populations and outcomes, the available evidence suggested no benefit from vitamin D screening (low-quality evidence) or was insufficient to permit conclusions.

Key Gaps in the Evidence

- No trials designed to assess the direct effect of vitamin D screening or testing on health outcomes, patient behavior, or clinical decision making.
- Insufficient evidence to establish precise values for optimal serum levels of vitamin D.
- Missing data regarding the differential effectiveness of supplementation according to baseline serum 25-OHD levels.
- Few supplementation trials in healthy older populations using current IOM-recommended doses of vitamin D and representing a wide range of baseline serum vitamin D values.
- Little epidemiological evidence and few supplementation trials in younger populations, pregnant or lactating women, and subgroups defined by ethnicity and race.

Other Considerations

- The practice guidelines, public policy statements, and payer policies reviewed do not support routine vitamin D screening.
- Screening in populations likely to have low vitamin D status may be helpful in promoting adherence to prescribed supplementation. However, there is no evidence that testing per se encourages adherence.

BACKGROUND

This section covers the following topics:

Vitamin D and Health Disorders
Definition of Vitamin D Deficiency
Prevalence of Vitamin D Deficiency
Vitamin D Biochemistry
Rationale for Testing, Monitoring, and Screening
Treatment of Insufficiency
Measurements Involved in Testing and Monitoring
Recommended Intake
Vitamin D Toxicity
Policy Context

Vitamin D and Health Disorders

Clinical Conditions That May Result from Vitamin D Deficiency

Examples of disorders that have traditionally been understood to be *caused by* vitamin D insufficiency are related to bone health. They include rickets, osteomalacia, and osteoporosis. Vitamin D insufficiency may also affect muscle strength, possibly through the mediation of vitamin D receptors, which decline with age, in skeletal muscle. Thus, falls as well as fractures may be patient-important results of vitamin D insufficiency (Hanley et al., 2010; Kennel et al., 2010; Bell, 2011).

Accumulating evidence suggests that the effects of vitamin D insufficiency are protean, i.e., that they are manifest in multiple organs and systems, not just in musculoskeletal tissue. For diseases such as cancer (especially colon, breast, and prostate cancers), cardiovascular disease, infection, allergies, type 1 and 2 diabetes, and multiple sclerosis and other autoimmune diseases, vitamin D insufficiency has been implicated as a risk factor for development of disease, but the mechanism of action is less clear than it is for the effect of vitamin D on musculoskeletal health. As with skeletal muscle, the link most likely relates to presence of vitamin D receptors and the enzymes required for vitamin D synthesis and catabolism in the skin, colon, prostate, breast, pancreas, heart, and components of the immune system. Calcitriol, which is the active metabolite of ingested and cutaneous vitamin D, occurs in these various tissues. Calcitriol helps determine gene expression and is thought to play various regulatory roles through gene expression (Wang, 2009; Hanley et al., 2010; Kennel et al., 2010; Bell, 2011).

Evidence suggests that vitamin D inhibits adaptive immunity while promoting innate (nonspecific) immunity and inhibiting inflammatory processes. Vitamin D also helps maintain barriers to infection in the gut, lung, placenta, and skin by increasing the production of a bactericidal protein called cathelicidin. Vitamin D has been shown to provide antiproliferative effects while stimulating cell differentiation. Antiproliferative effects include inhibition of telomerase expression, apoptosis, and angiogenesis, combined with promotion of gene expression associated with DNA repair. Thus, vitamin D may play a role in preventing autoimmune disease, infectious disease, and cancer (Hanley et al., 2010; Bell, 2011; Chung et al., 2011).

With respect to cardiovascular disease, there is evidence that good vitamin D status and/or supplementation is linked to reduction in blood pressure, increase in total high-density lipoprotein (HDL) levels, and reduction in markers for atherosclerosis and ventricular dysfunction. The connection between vitamin D and type 1 diabetes is assumed to be related to autoimmunity to pancreatic beta cells. Several mechanisms are thought to contribute to the link between vitamin D and type 2 diabetes. The evidence suggests that vitamin D promotes glucose-stimulated insulin release; furthermore, since vitamin D is a fat-soluble molecule, the additional muscle fat associated with metabolic syndrome leads to vitamin D depletion. There is also evidence that, in patients who have diabetes, vitamin D insufficiency contributes to the incidence of diabetic nephropathy and diabetic cardiovascular disease (CVD) (Bell, 2011).

Through its regulation of nerve function, vitamin D may help control some forms of muscle weakness and pain, and through its regulation of cartilage and articular bone formation, may thus reduce the risk of osteoarthritis (Bell, 2011).

Clinical Conditions That May Cause Vitamin D Deficiency

Some diseases, notably chronic kidney disease (CKD) and sarcoidosis, can cause vitamin D depletion. Patients with CKD have decreased conversion of serum 25-hydroxyvitamin D (25-OHD) to 1,25-dihydroxyvitamin D (1,25-[OH]2-D) as a result of impaired renal 1-hydroxylases activity, leading to secondary hyperparathyroidism and metabolic bone disease. Because of the liver's role in vitamin D metabolism, hepatic dysfunction might also lead to deficiency. Conditions that cause malabsorption and certain treatments can also result in vitamin D deficiency (Cannell and Hollis, 2008; Wang, 2009; Kennel et al., 2010).

Definition of Vitamin D Deficiency

Vitamin D stores derive from cutaneous production in response to sun exposure and, to a lesser extent, from dietary sources. Historically recommended daily intakes of vitamin D are often not adequate if sunlight exposure is limited. The wintertime sunlight in regions higher than 35 degrees latitude, which would include the state of Washington and most of the mainland United States, does not include enough ultraviolet B (UVB) radiation to stimulate cutaneous vitamin D production. Furthermore, factors such as the time of day of sunlight exposure, clothing, sunscreen use, pigmentation, and age influence UVB absorption and the effectiveness of sun exposure so that even individuals who live in sunny climates may be at risk of vitamin D insufficiency (IOM, 2011; Looker et al., 2011). Skin pigmentation affects risk because melanin reduces the synthesis of the precursor to vitamin D. The capacity to cutaneously produce vitamin D diminishes with age and is reduced by an estimated 75% by age 65 years (Cannell and Hollis, 2008; Wang, 2009; Hanley et al., 2010; Aloia, 2011; Bell, 2011; IOM, 2011). (NOTE: The phrase *at risk of vitamin D insufficiency* is used because individuals who have risk factors associated with lower levels of vitamin D do not necessarily have serum levels below a certain cutoff value. The phrase also acknowledges that the same concentration of serum vitamin D may be inadequate in some individuals and adequate in others.)

Additional factors affect vitamin D status. Breastfed infants are more likely than formula-fed infants to have vitamin D deficiency. National surveys have shown a greater risk of insufficiency or deficiency in females compared with males. In Western cultures, obesity is the most common cause of vitamin D deficiency. Obesity and vitamin D deficiency are linked because as a fat-soluble molecule, vitamin D is easily sequestered within adipose tissue. Lastly, high heritability of vitamin D insufficiency suggests that

genetic determinants may also play a role. A genome-wide association study of 25-OHD among approximately 30,000 individuals of European descent from 15 cohorts showed that variants near genes involved in cholesterol synthesis (DHCR7), hydroxylation (CYP2R1, CYP24A1), and vitamin D transport (GC) influence vitamin D status. Genetic variation at these loci identifies individuals of European descent who have substantially elevated risk of vitamin D insufficiency (Cannell and Hollis, 2008; Wang, 2009; Kennel et al., 2010; Looker et al., 2010; Aloia, 2011; Bell, 2011).

Prevalence of Vitamin D Deficiency

Data for the years 2001 to 2006 from the periodic National Health and Nutrition Examination Survey (NHANES) revealed that approximately one third (33%) of the U.S. population was at risk of vitamin D *insufficiency*, defined by the Institute of Medicine (IOM) as serum levels of 25-OHD < 50 nanomoles per liter (nmol/L) (20 nanograms per milliliter [ng/mL]). Although median serum levels fell within the sufficiency range for all subgroups defined by age, sex, and pregnancy/lactation status, the risk of vitamin D deficiency or insufficiency did differ according to these factors and according to race and ethnicity. The season-adjusted prevalence of the risk of vitamin D *deficiency* (serum 25-OHD < 30 nmol/L) ranged from 1% to 8% in men and from 1% to 12% in women, depending on age, and the prevalence of the risk of *insufficiency* from 9% to 28% in men and 11% to 28% in women. Overall, females were more likely than males to be at risk of deficiency (10% versus 6%), but the overall difference in risk of insufficiency was negligible. The risk of both deficiency and insufficiency peaked at age 30 years in males and then decreased slightly and remained stable thereafter with increasing age. Data for females showed significant increases in risk of deficiency and insufficiency in adolescent subgroups, a slight nonsignificant increase in risk of deficiency by age 50, a small but significant increase in risk of insufficiency by age 70, and stable values after age 70 years. The risk of vitamin D deficiency or insufficiency was the lowest among children aged 1 to 8 years. Non-Hispanic black or Mexican ethnicity was associated with greater prevalence of a risk of both deficiency and insufficiency, while pregnancy and lactation reduced the risks (Looker et al., 2011). The NHANES report did not provide vitamin D insufficiency data by state and no data specific to the general population of Washington State were identified in the published literature.

Many laboratories that offer vitamin D testing use cutoff values that are much higher than the 50 nmol/L or 20 ng/mL recommended by the IOM and the IOM thus advises that some estimates of the prevalence of vitamin D insufficiency may be inflated (IOM, 2011). Furthermore, since the 50 nmol/L threshold corresponds to a level that is sufficient for almost all individuals in a general population (97.5%) and thus is more than sufficient for many, the NHANES estimates referred to previously pertain to the proportion of the population *at risk* of insufficiency or deficiency, not the proportion of individuals who actually have poor vitamin D status. NHANES data do indicate that, in general, vitamin D status deteriorated in the U.S. population between the 1988-1994 and 2001-2002 surveys, according to the current IOM thresholds, but there was no change from 2001-2002 to 2005-2006 (Looker et al., 2011).

See **Measurements Involved in Testing and Monitoring**, *Optimal Serum 25-OHD Levels*.

Vitamin D Biochemistry

Vitamin D is a steroidal hormone that regulates the homeostasis of calcium and phosphorus with its final metabolic product targeting > 200 human genes in a wide variety of tissues. It exists in two common forms: D2 (ergocalciferol, also called calciferol) and D3 (cholecalciferol). Of the two forms, D3 increases

serum 25-OHD more efficiently. Vitamin D3 can be obtained from dietary sources or from biosynthesis in the skin from its precursor through UVB irradiation. Vitamin D2 is derived from yeast, in which vitamin D is produced from irradiation of ergosterol, and from plant sources. Both D2 and D3, which are sometimes referred to as *inactive vitamin D*, follow the same metabolic pathway and are modified in the liver to form 25-OHD. Serum 25-OHD is the principal form of vitamin D storage in the body. In the kidney further metabolism produces the *active* hormone 1,25-(OH)2-D, also known as calcitriol. Calcitriol is essential for the efficient active absorption of dietary calcium and phosphate. Serum 25-OHD has a long half-life and except in individuals with sarcoidosis or rare disorders of phosphate or vitamin D metabolism, serum 25-OHD rather than 1,25-(OH)2-D is the appropriate marker for serum tests of vitamin D sufficiency (Clive et al., 2002; Cannell and Hollis, 2008; Hollis, 2008; Hanley et al., 2010; Kennel et al., 2010; Wang et al., 2009; Bell, 2011; Yuan et al., 2011).

Serum 25-OHD positively promotes intestinal absorption of calcium. Insufficient levels of serum 25-OHD can cause secondary hyperparathyroidism through a reduction in serum calcium and consequent excessive production of parathyroid hormone (PTH), which in turn stimulates bone resorbing osteoclast activity to raise the calcium concentrations in the serum back to normal. These mechanisms explain the link between vitamin D and bone health (Wang, 2009; Kennel et al., 2010).

Calcitriol as well as synthetic vitamin D analogs may be administered as pharmaceuticals. They are not considered dietary supplements. Like calcitriol, synthetic analogs are considered to be active forms of vitamin D. Examples include dihydrotachysterol (DHT), alfacalcidiol (1α-(OH)D3), calcipotriol, tacalcitol, 19-nor-1,25(OH)2D2 (19-norD2), oxacalcitriol (OCT), 22-oxa-1,25(OH)2D3, paricalcitol, doxercalciferol, 1α-hydroxyvitamin D2 (1α-(OH)D2), and falecalcitriol (Seely et al., 2012).

Box 1. Chemical Names for Vitamin D

Inactive Forms: cholecalciferol (vitamin D3), ergocalciferol or calciferol (vitamin D2), serum 25-hydroxyvitamin D (25-OHD)

Active Natural Analog: calcitriol (1,25-[OH]2-D)

Active Synthetic Analogs: 1α-hydroxyvitamin D2 (1α-(OH)D2), 19-nor-1,25(OH)2D2 (19-norD2), 22-oxa-1,25(OH)2D3, alfacalcidiol (1α-(OH)D3), calcipotriol, dihydrotachysterol (DHT), doxercalciferol, falecalcitriol, oxacalcitriol (OCT), paricalcitol, tacalcitol

Rationale for Testing, Monitoring, and Screening

Several *clinical factors* suggest the potential for vitamin D insufficiency or deficiency and thus may be indicators for vitamin D *testing*. Relevant conditions include poor nutrition, malabsorption due to gastrointestinal disease or malabsorptive bariatric surgery, hepatic dysfunction, and renal dysfunction or age-related renal changes. Laboratory findings that suggest possible vitamin D deficiency include low urine calcium excretion, elevated parathyroid hormone level, elevated alkaline phosphatase, lower serum calcium, and low serum phosphorous. Radiographic findings that might raise suspicion of deficiency include osteopenia/osteoporosis, nontraumatic fracture, and skeletal pseudofracture. If testing is performed because of a serious chronic disease such as CKD, testing and follow-up may be most appropriately managed by the specialist caring for that problem (Hanley et al., 2010; Kennel et al., 2010).

In the absence of clinical indicators, vitamin D testing would be considered *screening*. The purpose of screening would be to assess the need to improve vitamin D status as a preventive measure against health problems (see **Vitamin D and Health**). Screening in healthy populations could be universal (routine), or it could be based on demographic or lifestyle factors that are associated with low serum vitamin D (high risk). Screening in populations defined by the presence of diseases such as cancer or diabetes would be for the purpose of assessing the need to improve vitamin D status as a way of improving disease-related outcomes. Vitamin D screening is more controversial than vitamin D testing.

The 2010 IOM report (see **Measurements Involved in Testing and Monitoring**, *Optimal Serum 25-OHD Levels* and **Recommended Intake**) did not include recommendations on when testing should be performed to determine serum 25-OHD levels. Thus, the question of selective screening of subgroups to determine the need for supplementation or increases in supplementation has not been answered (Aloia, 2011).

Treatment of Insufficiency

Current Practice

Treatment of vitamin D insufficiency or deficiency may serve to prevent, ameliorate, or cure disease. Vitamin D deficiency can be treated by sunlight, artificial UVB light, changes in diet, and vitamin D supplementation. Sunlight exposure carries with it the risk of skin cancer. Achieving optimal vitamin D levels with diet is difficult since fatty fish is the only food rich in vitamin D (even dairy products and fortified foods provide low quantities). Supplements, on the other hand, are inexpensive and considered to be safe. Several negative feedback mechanisms in the human body help guard against vitamin D toxicity (Kennel et al., 2010; Bell, 2011).

Prescribed vitamin D supplementation regimens typically start with a very large loading dose administered over several weeks, followed by a maintenance dose. Oral administration may have to involve especially high dosages for individuals in extreme malabsorptive states. Intramuscular formulations are available from compounding pharmacies but are otherwise not available in the United States. Supplements providing D2 and D3 are comparably effective in raising serum levels, but the half-life of D3 is greater and requires less frequent dosing (Kennel et al., 2010).

The IOM's Dietary Reference Intake (DRI) values for vitamin D intake in generally healthy populations are designed to serve the needs of almost all (97.5%) individuals, regardless of sun exposure (see **Recommended Intake**). However, individual response to a particular therapeutic level of supplementation can vary (Wang, 2009; Chung et al., 2011).

Impact on Serum Levels

According to systematic reviews conducted for the Agency for Healthcare Research and Quality (AHRQ), good evidence demonstrates that, in adults, serum 25-OHD levels rise with increased dietary intake of vitamin D from fortified foods (Cranney et al., 2007; Chung et al., 2009). Chung et al. (2009) also provided data from 26 placebo-controlled supplementation randomized controlled trials (RCTs) in which

treatment groups received vitamin D supplementation with or without calcium. Overall, the evidence shows that serum 25-OHD levels in adults and in children rise with vitamin D supplementation and that the magnitude of the effect of supplementation on serum levels increases with dosage and duration of supplementation and may be somewhat greater when baseline serum levels are lower. Details from the 2009 analysis by Chung and colleagues follow.

In adults taking standard doses of 400 to 800 international units per day (IU/day), the mean improvement from baseline ranged from 8.4 to 65.0 nmol/L, while in corresponding placebo groups the mean change was –9.2 to 9.3 nmol/L (13 RCTs, total n=580). Mean baseline serum levels were 23 to 74 nmol/L overall in the study groups. In other adult studies where treatment groups received higher doses (880 to 5000 nmol/L), mean improvement in the treatment groups ranged from 12.1 to 91.9 nmol/L, while change in the corresponding placebo groups ranged from –15.0 to 18 nmol/L (11 RCTs, total n 764). Again, mean baseline serum values varied widely, from 23 to 71 nmol/L. The difference in change between the treatment and placebo groups was not always statistically significant, but the differences across all 26 trials always favored the treatment group, regardless of dose (200 IU/day for 1 year to 5000 IU/day for 5 months). In the 9 studies where baseline serum levels were in the range understood by the IOM to represent risk of deficiency (< 30 nmol/L); follow-up levels were in the IOM-defined sufficiency range (> 50 nmol/L). Regimens in these 9 studies ranged from 300 IU/day for 1 year to 2000 IU/day for 1.5 months. No pattern with respect to whether study groups included all adults or only adults > 70 years of age is discernible (Chung et al., 2009).

In 3 RCTs (total, n=283) involving children, changes favored the supplementation groups but were not statistically significant at doses of 200, 400,and 2000 nmol/L, administered ≥ 6 months. Baseline serum values were 35 to 43 nmol/L (Chung et al., 2009).

Chung et al. (2009) demonstrated graphically (not mathematically) that supplementation effects may be somewhat greater in groups where mean baseline 25-OHD is ≤ 40 nmol/L and when the duration of supplementation exceeds 3 months.

Measurements Involved in Testing and Monitoring

Target Molecule

Since all ingested and cutaneously produced vitamin D is converted to 25-OHD, measuring and properly interpreting the circulating 25-OHD concentrations is the generally accepted measure of vitamin D status. Quantification of 25-OHD2 and 25-OHD3 fractions may facilitate treatment monitoring; e.g., lack of increase in 25-OHD2 or 25-OHD3 and total 25-OHD levels after D2 or D3 supplementation may indicate inadequate dosing, non-adherence, or malabsorption. It is crucial to remember that serum 1,25-(OH)2-D (calcitriol) levels play no role in diagnosing vitamin D deficiency because the kidney tightly controls its levels, which are often normal or even elevated in the presence of vitamin D deficiency. Therefore, a patient with normal or high 1,25-(OH)2-D serum levels but low 25-OHD levels is vitamin D deficient despite high serum levels of the active hormone. Also, 1,25-(OH)2-D measurement is very challenging since the majority of circulating 1,25-(OH)2-D is bound to vitamin binding protein (VBP) and albumin and since various other substances in serum interfere (Clive et al., 2002; Cannell and Hollis, 2008; Kennel et al., 2010; Lai et al., 2010; Yuan et al., 2011).

A special issue is involved in testing serum from neonates, which uniquely contains a molecule, the 3-epimer 25-OHD3 molecule (3-epi-25-OHD3), having the same mass as 25-OHD3. Thus, serum testing in

neonates should be performed by methods that do not detect 25-OHD3 or allow an adjustment in the results (Carter, 2011).

Given the half-life of 25-OHD and the time required for serum increases to plateau, patients who have been prescribed standard-dose supplementation need not be monitored any sooner than 3 months after initiation of treatment. However, testing after 1 month may be appropriate for patients receiving doses exceeding 2000 IU per day (Hanley et al., 2010). See **Recommended Intake** for the standard and upper tolerable dosages defined by the IOM.

Optimal Serum 25-OHD Levels

Population-based reference ranges can suggest different normal value ranges for different ethnicities, age groups, geographic locations, and seasons of the year. Thus, rather than establishing such reference ranges, cutoff values have been defined that correspond to thresholds for clinical decision making. Some experts, looking at physiological rationale, have advocated a cutoff value of 75 nmol/L for identifying individuals with insufficient serum 25-OHD levels, at least for prevention and treatment of osteoporosis. This opinion reflects early evidence that 75 nmol/L represents the minimum level for suppression of parathyroid hormone (and thus prevents hyperparathyroidism) and also represents the concentration that maximizes intestinal calcium absorption. The recent IOM committee, however, concluded that evidence pertaining to parathyroid hormone suppression was inconsistent, and according to national surveys, serum levels 30 to 50 nmol/L or higher were sufficient for maximum skeletal calcium absorption in children and adults (Kennel et al., 2010; Aloia, 2011).

Thus, in its latest report on DRIs for vitamin D, the IOM advised that 50 nmol/L (20 ng/mL) was the appropriate cutoff value for good bone health (IOM, 2011). The IOM recognizes the risk categories outlined in Box 2.

Box 2. Vitamin D Thresholds Defined for Good Bone Health by the IOM

Possibly harmful: > 125 nmol/L (50 ng/mL)

Sufficient: ≥ 50 nmol/L (20 ng/mL)

At risk of insufficiency: < 50 nmol/L (20 ng/mL)

At risk of deficiency: < 30 nmol/L (12 ng/mL)

The IOM report expressed concern that the prevalence of vitamin D deficiency has been overestimated since most laboratories use cutpoints higher than 50 nmol/L to define sufficiency. On the other hand, optimal levels may depend on the disease or disorder that is of interest in preventive medicine (Kennel et al., 2010). It is important to remember that serum thresholds and DRI values set by the IOM refer only to bone health and only to individuals who do not have a disease that puts them at risk of vitamin D insufficiency (Aloia, 2011; Bell, 2011; IOM, 2011).

See also **DESCRIPTION** for a discussion of assays.

Recommended Intake

Exposure to sunshine (except in the winter in northern latitudes) is the most efficient way of improving vitamin D stores: 20 minutes of sunshine generates 5 times more vitamin D3 than would consumption of 3.5 ounces of salmon. However, skin cancer risks dictate that sun exposure be minimized. Thus, combined intake from food and supplements should be the preventive treatment strategy. In patients who have been diagnosed with vitamin D deficiency, doses of 50,000 to 100,000 IU weekly are typically prescribed and continued for approximately 3 months. The same dose is then administered monthly, or according to the frequency suggested by monitoring of serum 25-OHD (Bell et al., 2010).

DRIs, which are established by the IOM, include four values (Health Canada, 2010; Aloia, 2011):

> Estimated Average Requirement (EAR): A literature-based estimate of the amount required to promote health in half of all healthy individuals in a particular age and gender group.
>
> Recommended Dietary Allowance (RDA): The average dietary intake that is sufficient to meet the needs of nearly all (97.5%) healthy persons, calculated from the EAR.
>
> Adequate Intake (AI): Established only when there is insufficient scientific evidence to establish an EAR and an RDA. It may be derived from experimental data, or it may simply represent the observed average intake of a group of healthy people.
>
> Tolerable Upper Intake Level (UL): The highest daily intake that is unlikely to create a risk of adverse health effects for almost any individual.

From a population perspective, where a distribution of values is the focus, the EAR is the appropriate value. From an individual perspective, the RDA is the appropriate value, although it actually represents more than adequate intake for many people. In other words, not all individuals require the same intake for the same measure of health. This is because not all individuals require the same serum concentration of 25-OHD for the same measure of health (Aloia, 2011).

The current IOM recommendations regarding DRIs represent a collaborative effort, begun in 2008, between the United States and Canada to update the DRIs that were published in 1994 (Aloia, 2011). Prior to this project, evidence was lacking for the establishment of EARs or RDAs, and the IOM had provided only AIs (Cranney et al., 2007). Using the findings of the first two AHRQ reports on the subject (Cranney et al., 2007; Chung et al., 2009), the IOM chose bone health as the best indicator for setting the new DRIs and then used dose-response data from those reports to establish values for the different DRI measures. The bone health measures considered by the IOM were calcium absorption, calcium retention, bone mineral density, rickets, osteomalacia, and fracture. The IOM concluded that for nonskeletal health indicators, the evidence did not demonstrate causality, was inconsistent, and/or did not reveal a dose-response relationship. The current DRIs resulting from that report are outlined in Box 3 (Aloia et al., 2011; IOM, 2011):

Box 3. Current IOM Daily Recommended Intake (DRI) Values

RDA for adults and children: 600 IU/day, corresponding to serum levels of 50 nmol/L and reflecting an EAR established with dose-response data for bone health.

AI for infants: 400 IU/day, based on observed average for infants without evidence of rickets.

RDA for individuals > 70 years of age: 800 IU/day, corresponding to 73 nmol/L and reflecting dose-response data. The higher target level for serum concentration reflects a consideration of the heterogeneity in this population and the consequences of insufficiency.

UL: 4000 IU/day for children > 8 years of age and for adults. See **Vitamin D Toxicity** for additional details.

Individuals who live in northern latitudes, use sunscreen, or wear clothing that does not allow sun exposure need not take supplements in excess of the IOM recommendations since the recommendations presume minimal or no sunlight exposure. By the same token, the DRIs might be high for individuals who have high sunlight exposure. Obese individuals might need greater intake because excess adipose tissue reduces the availability of 25-OHD. There is some preliminary evidence that the optimal serum level of 25-OHD in African-Americans is lower than in other ethnic groups, and although cutaneous manufacture of vitamin D is reduced in this population, the level required for both disease prevention and avoidance of vitamin D toxicity is lower (Aloia, 2011).

Vitamin D Toxicity

The harms associated with vitamin D toxicity include kidney and other tissue damage, as well as kidney stones. Hypercalcemia and hypercalciuria are considered indicators of vitamin D toxicity. The daily upper level intake (ULI) values set by the IOM are 1000 IU per day (IU/day) for infants ≤ 6 months, 1500 IU/day for infants 6 to 12 months, 2500 IU/day for children aged 1 to 3 years, 3000 IU/day for children ages 4 to 8 years, and 4000 IU/day for children > 8 years and for adults. Available data defined 10,000 IU/day as the maximum dose corresponding to a no observed adverse event level (NOAEL). However, the UL was set considerably lower than 10,000 IU because of the lack of data on long-term adverse events associated with very high doses of vitamin D. The 4000 IU/day recommendation corresponds to a serum 25-OHD level of 125 nmol/L and takes into account a possible J-shaped or U-shaped response curve with respect to the relationships between serum 25-OHD and the incidence of falls and fracture, all-cause mortality, cardiovascular disease, and cancer, as well as bone health (Kennel et al., 2010; Aloia, 2011; Bell, 2011; IOM, 2011).

Policy Context

The wide range of health outcomes with which vitamin D has a purported but unproven relationship suggests the potential for overutilization. Key public health organizations in the United States and Canada have concluded that valid serum cutoff values have not been established for specific health outcomes and/or that routine testing of vitamin D serum levels is not warranted. The Washington Health Care Authority can benefit from an analysis of evidence regarding the association of vitamin D with health outcomes and the utility of screening in general populations, as well as populations with chronic disease.

Agency Data

Section 1: Agency usage, Vitamin D Testing

Section 1 displays basic costs, counts and trends, using the paid amount for each claim, affording a summary of agency expenditures and number of patients served. Patient cost-sharing and coordination of benefits between other payers results in lower average payments compared to actual treatment costs (Section 2- Allowed amount).

Figure 1.1 Vitamin D Overall Payments by Agency –2008-2011

Agency/Year	2008	2009	2010	2011	4 Yr Overall Total[1]	Avg % Change	
PEB[2]							
Agency Population	204,804	210,501	213,487	212,596		1.30%	
Patient Ct (% of Total Pop.)	14042 (6.9%)	24892 (11.8%)	30794 (14.4%)	27884 (13.1%)	62537	28.50%	*
Amount Paid	$794,264	$1,394,316	$1,541,307	$1,032,884	$4,762,771	15.70%	*
Average Paid per Patient	$57	$56	$50	$37	$76	-12.50%	
95% upper limit per pt	$154	$152	$141	$104	$246		
Average Tests per Patient (95% upper limit per pt)	1.3 (2.7)	1.3 (2.6)	1.2 (2.4)	1.2 (2.3)	1.9 (5.0)		
Average Paid/Test	$44	$44	$40	$31	$39	-10.30%	
Medicaid							
Agency Population	392,808	416,871	424,230	435,187		3.50%	
Patient Ct (% of Total Pop.)	6849 (1.7%)	14874 (3.6%)	21450 (5.1%)	21432 (4.9%)	48,870	47.90%	*
Amount Paid	$340,609	$707,391	$975,272	$897,564	$2,920,835	40.30%	*
Average Paid per Patient	$50	$48	$45	$42	$60	-5.60%	
95% upper limit per Patient	$130	$123	$124	$123	$208		
Average Tests per Patient (95% upper limit per pt)	1.3 (2.7)	1.3 (2.7)	1.3 (2.7)	1.3 (2.7)	1.7 (4.7)		
Average Paid/Test	$38	$37	$35	$32	$35	-5.60%	
L&I[3]							
Patient Ct	133	60	67	57	295	-19.4%	
Amount Paid	$12,407	$4,294	$4,886	$4,521	$26,109	-19.7%	
Average Paid per Patient	$93	$72	$73	$79	$89	-4.2%	
Average Tests per Patient	1.2	1.0	1.0	1.0	1.1	-5.3%	
Average Paid/Test	$62	$61	$62	$67	$63	2.7%	

*Average % Change adjusted for population growth

[1] Patients who receive tests in multiple years are counted once in the 4 Yr Overall Total

[2] Public Employee Benefits

[3] Labor and Industries usage is low compared to other agencies, so is not analyzed further

Vitamin D test CPT codes used in analysis: 82306 (Vitamin D, 25 hydroxy), 82652 (Vitamin D1, 25-dihydroxy). CPT 82306 is the predominantly used code.

CPT 82652 tests

Agency	% Total Tests	% Total Payments
PEB	4.2%	3.5%
Medicaid	4.1%	3.6%
L&I	16.9%	19.5%

Figure 1.2a: PEB Vitamin D Testing – Utilization by Age and Gender

# by Age Group	2008	2009	2010	2011	4 Yr Overall[1]
Total	**14042**	**24892**	**30794**	**27884**	**62537**
0-17	277	464	736	735	**1774**
18-34	1221	2518	3148	3229	**7513**
35-49	3303	6421	8065	7223	**15946**
50-64	7854	13126	15946	13636	**30183**
65-79	1252	2115	2626	2716	**6322**
80+	135	248	273	345	**799**
% Female	**2008**	**2009**	**2010**	**2011**	**4 Yr Overall[1]**
% of Total	78%	76%	72%	72%	**72%**
0-17	57%	60%	58%	56%	**57%**
18-34	81%	82%	79%	78%	**78%**
35-49	81%	79%	76%	75%	**76%**
50-64	79%	76%	72%	71%	**72%**
65-79	67%	62%	59%	61%	**61%**
80+	70%	63%	64%	64%	**65%**

[1]Patients who receive tests in multiple years are counted once in the 4 year overall total.

Figure 1.2b: Medicaid - Utilization by Age and Gender

Age Group	2008	2009	2010	2011	4 Yr Overall[1]
Total	**6849**	**14875**	**21450**	**21432**	**48870**
0-17	632	1385	1963	2370	**4995**
18-34	1106	2855	4557	4344	**10854**
35-49	1795	3934	5711	5318	**12464**
50-64	2751	5791	8116	7940	**17209**
65-79	476	752	907	1161	**2713**
80+	89	158	196	299	**635**
% Female	**2008**	**2009**	**2010**	**2011**	**4 Yr Overall[1]**
Total	**74%**	**71%**	**70%**	**68%**	**69%**
0-17	47%	54%	52%	51%	**52%**
18-34	76%	75%	74%	74%	**75%**
35-49	76%	73%	70%	70%	**70%**
50-64	77%	71%	70%	69%	**69%**
65-79	78%	74%	70%	69%	**71%**
80+	75%	70%	69%	69%	**71%**

[1]Patients who receive tests in multiple years are counted once in the 4 Yr Overal total

Section 2: Agency usage, Vitamin D Testing

Investigation of per person charges use agency "Allowed" amounts so do not reflect patient cost-sharing or benefit coordination between payers.

Costs in the following tables are not comparable to Section I, which uses claim payments for estimation of future costs and decision impact.

Figure 2.1 Average Cost of Vitamin D Test, PEB Primary, Medicaid, 2008-2011

Per Treatment Average Allowed (% of tests)	PEB Primary	Medicaid
Overall Average	$55	$36
HOSPITAL	$67 (29%)	$40 (30%)
INDEPENDENT LAB	$50 (53%)	$34 (64%)
OFFICE	$54 (17%)	$40 (4%)

Medicaid and L&I published current maximum payments for Vitamin D tests:

Agency	CPT 82306	CPT 82652
Medicaid[1]	$32.29	$41.99
L&I[2]	$58.72	$75.29

[1]Medicaid Fee Schedule
[2]L&I Fee Schedule

Figure 2.2a PEB Top 50* Diagnoses for Vitamin D Tests by Frequency (2008-2011)

Dx Code and Description		Allowed Amount	Count	Cumula-tive % Procs	Dx Code and Description		Allowed Amount	Proc. Count	Cumula-tive % Procs
All Tests		**$6,677,275**	**121788**						
V70.0	ROUTINE MEDICAL EXAM	$1,041,581	20924	17.2%	**311**	DEPRESSIVE DISORDER NEC	$34,251	631	68.4%
268.9	VITAMIN D DEFICIENCY NOS	$625,897	11545	26.7%	**V72.60**	LAB EXAM, UNSPECIFIED	$32,304	579	68.9%
780.79	MALAISE AND FATIGUE NEC	$454,822	8331	33.5%	**790.6**	ABN BLOOD CHEMISTRY NEC	$32,181	562	69.4%
272.4	HYPERLIPIDEMIA NEC/NOS	$344,657	6137	38.5%	**245.2**	CHR LYMPHOCYT THYROIDIT	$22,016	415	69.7%
244.9	HYPOTHYROIDISM NOS	$288,744	5337	42.9%	**340**	MULTIPLE SCLEROSIS	$27,860	404	70.0%
V72.31	ROUTINE GYN EXAMINATION	$210,201	4159	46.3%	**790.21**	IMPAIRED FASTING GLUCOSE	$20,676	393	70.3%
250	DMII WO CMP NT ST UNCNTR	$162,638	2938	48.7%	**V82.9**	SCREEN FOR CONDITION NOS	$18,551	391	70.6%
401.1	BENIGN HYPERTENSION	$156,608	2895	51.1%	**719.49**	JOINT PAIN-MULT JTS	$21,265	386	70.9%
272	PURE HYPERCHOLESTEROLEM	$124,533	2314	53.0%	**V72.6**	DEL - LABORATORY EXAM	$22,095	377	71.2%
401.9	HYPERTENSION NOS	$116,982	2132	54.8%	**V77.91**	SCREEN LIPOID DISORDERS	$19,049	377	71.5%
733.9	BONE & CARTILAGE DIS NOS	$95,990	1741	56.2%	**733.01**	SENILE OSTEOPOROSIS	$18,916	324	71.8%
V58.69	LONG-TERM USE MEDS NEC	$94,080	1696	57.6%	**V72.62**	ROUTINE LAB EXAM	$13,914	317	72.1%
174.9	MALIGN NEOPL BREAST NOS	$117,140	1680	59.0%	**789**	ABDMNAL PAIN UNSPCF SITE	$18,080	316	72.4%
272.2	MIXED HYPERLIPIDEMIA	$82,670	1493	60.2%	**585.6**	END STAGE RENAL DISEASE	$33,414	315	72.7%
627.2	SYMPT FEM CLIMACT STATE	$70,333	1295	61.3%	**714.9**	INFLAMM POLYARTHROP NOS	$16,464	300	72.9%
733	OSTEOPOROSIS NOS	$64,706	1177	62.3%	**V76.44**	SCRN MALIG NEOP-PROSTATE	$12,207	299	73.1%
285.9	ANEMIA NOS	$56,963	1047	63.2%	**257.2**	TESTICULAR HYPOFUNC NEC	$15,026	283	73.3%
280.9	IRON DEFIC ANEMIA NOS	$44,345	809	63.9%	**185**	MALIGN NEOPL PROSTATE	$14,888	280	73.5%
729.1	MYALGIA AND MYOSITIS NOS	$44,098	761	64.5%	**269.2**	VITAMIN DEFICIENCY NOS	$15,324	273	73.7%
579.3	INTEST POSTOP NONABSORB	$50,377	739	65.1%	**790.29**	ABNORMAL GLUCOSE NEC	$14,920	273	73.9%
250.02	DMII WO CMP UNCNTRLD	$39,727	731	65.7%	**719.4**	JOINT PAIN-UNSPEC	$15,294	268	74.1%
714	RHEUMATOID ARTHRITIS	$37,456	694	66.3%	**V70.9**	GENERAL MEDICAL EXAM NOS	$13,664	268	74.3%
244.8	ACQUIRED HYPOTHYROID NEC	$36,992	687	66.9%	**530.81**	ESOPHAGEAL REFLUX	$12,855	241	74.5%
585.3	CHR KIDNEY DIS STAGE III	$37,130	669	67.4%	**V22.1**	SUPERVIS OTH NORMAL PREG	$12,570	240	74.7%
V77.99	SCREEN-ENDOC/NUT/MET	$29,126	641	67.9%	**278.01**	MORBID OBESITY	$11,648	240	74.9%

***2503 diagnosis codes were used on PEB claims for Vitamin D tests during 2008-2011**

Fig. 2.2b Medicaid Top 50* Diagnoses for Vitamin D Tests by Frequency (2008-2011)

Dx Code and Description		Allowed Amount	Proc. Count	Cum. % Procs	Dx Code and Description		Allowd Amount	Proc. Count	Cum. % Procs
All Tests		**$3,024,254**	**84278**						
268.89	Vitamin D deficiency NOS	$270,031	7768	8.9%	**42.42**	Human immuno virus dis	$16,412	481	52.2%
780.79	Malaise and fatigue NEC	$194,619	5109	15.4%	**724.42**	Lumbago	$16,207	447	52.7%
250.00	DMII wo cmp nt st uncntr	$136,482	3844	19.9%	**719.49**	Joint pain-mult jts	$15,438	449	53.2%
272.24	Hyperlipidemia NEC/NOS	$102,576	2807	23.3%	**588.81**	Sec hyperparathyrd-renal	$15,306	451	53.7%
585.56	End stage renal disease	$94,842	2465	26.4%	**733.90**	Bone & cartilage dis NOS	$15,204	387	54.2%
401.19	Hypertension NOS	$72,799	2068	28.8%	**780.39**	Convulsions NEC	$15,129	441	54.7%
401.11	Benign hypertension	$69,116	2004	31.1%	**340.40**	Multiple sclerosis	$15,028	436	55.2%
244.49	Hypothyroidism NOS	$66,321	1853	33.3%	**280.09**	Iron defic anemia NOS	$14,897	424	55.7%
V58.69	Long-term use meds NEC	$60,863	1709	35.3%	**V72.31**	Routine gyn examination	$14,320	421	56.2%
V22.21	Supervis oth normal preg	$54,875	1617	37.1%	**789.00**	Abdmnal pain unspcf site	$14,075	364	56.6%
729.91	Myalgia and myositis NOS	$41,365	1106	38.5%	**338.84**	Chronic pain syndrome	$13,335	385	57.1%
250.02	DMII wo cmp uncntrld	$40,937	1150	39.8%	**V58.83**	Therapeutic drug monitor	$13,249	253	57.5%
311.11	Depressive disorder NEC	$39,419	1140	41.1%	**296.80**	Bipolar disorder NOS	$12,286	351	57.9%
285.59	Anemia NOS	$39,168	1107	42.4%	**285.21**	Anemia in chr kidney dis	$11,539	299	58.3%
585.53	Chr kidney dis stage III	$38,711	1008	43.7%	**790.06**	Abn blood chemistry NEC	$10,622	301	58.7%
174.49	Malign neopl breast NOS	$35,866	1068	44.9%	**585.59**	Chronic kidney dis NOS	$10,598	270	59.0%
714.40	Rheumatoid arthritis	$35,348	1043	46.1%	**784.40**	Headache	$10,563	295	59.4%
733.00	Osteoporosis NOS	$26,855	746	47.0%	**729.95**	Pain in limb	$10,426	282	59.7%
272.20	Pure hypercholesterolem	$24,349	689	47.8%	**280.00**	Chr blood loss anemia	$9,854	238	60.0%
272.22	Mixed hyperlipidemia	$22,513	618	48.5%	**724.45**	Backache NOS	$9,791	273	60.3%
705.54	Chrnc hpt C wo hpat coma	$20,323	605	49.2%	**530.81**	Esophageal reflux	$9,595	274	60.7%
V20.02	Routin child health exam	$19,696	586	49.8%	**300.00**	Anxiety state NOS	$9,256	269	61.0%
V22.20	Supervis normal 1st preg	$19,511	569	50.5%	**710.00**	Syst lupus erythematosus	$9,243	265	61.3%
719.40	Joint pain-unspec	$17,172	411	51.0%	**250.01**	DMI wo cmp nt st uncntrl	$8,749	242	61.6%
585.54	Chr kidney dis stage IV	$17,047	429	51.6%	**783.21**	Abnormal loss of weight	$8,740	246	61.9%

***2806 diagnosis codes were used on Medicaid claims for Vitamin D tests during 2008-2011**

TECHNOLOGY DESCRIPTION

Serum 25-hydroxyvitamin D (25-OHD) assays fall into three general categories: competitive protein binding (CPB) assays, immunoassays, and chromatographic assays. There are commercially available kits, some of them with Food and Drug Administration (FDA) approval, within each category, but chromatography-based assays typically use "home-brew" processes (Carter, 2011). Box 4 lists specific assays under these three headings.

Box 4. 25-OHD Assays

Competitive Protein Binding (CPB) Assays

Chromatographic Assays: Usually developed in house, but commercial kits are available.

High performance liquid chromatography (HPLC): Sometimes referred to as HPLC/UV to signify its use of ultraviolet-based detection.
Liquid chromatography with mass spectrometry (LC-MS): Usually tandem mass spectrometry (LC-MS/MS).
Gas chromatography-mass spectrometry (GC-MS): Not available commercially and seldom used.

Immunoassays: Commercial assays
Radioimmunoassay (RIA)
Chemiluminescence assay
Enzyme immunoassay (EIA)
Electrochemiluminescence immunoassay

Source: Carter (2011)

Assays vary in their ability to detect 25-OHD2, as well as 25-OHD3, and their ability to differentiate between 3-epi-25-OHD (present only in neonatal serum and not considered to be a measure of vitamin D status) and 25-OHD. Different assay types produce discordant results when applied to the same human serum. An assessment of the accuracy of assays is hampered by the lack of a true reference standard. As one author has put it, "it is impossible know if any individual 25-OHD result is the true value" (Carter, 2011, p. 25). The first 25-OHD assays were CPB and chromatographic assays. Gas chromatography-mass spectrometry (GC-MS) was the earliest definitive test for 25-OHD but is no longer in use. Currently, authors refer to either the HPLC (Carter, 2011) or the LC-MS/MS (Wang, 2009) as the "gold standard." However, chromatography, as well as CPB methods, are time consuming and expensive; thus, manufacturers have developed immunoassays as cheaper alternatives.

Manufacturers of immunoassays may use LC-MS methods to calibrate their products because of the specificity that can be assumed for tandem mass spectrography. However, the DiaSorin RIA is also used to calibrate other types of immunoassays for 25-OHD (Carter, 2011).

A major systematic review conducted to inform U.S. public health policy reported that studies suggested variable cutoff values for assessing the risk of poor bone health because of possible assay imprecision and variability in methods (Cranney et al., 2007). Efforts are underway to establish a universally recognized reference standard. Even though it is typically a "home brew" process and thus not subject to FDA regulation, LC-MS/MS is expected to be accepted by the Joint Committee for Traceability in Laboratory Medicine as the Reference Measurement Procedure (RMP) for 25-OHD, in which case candidate LC-MS processes developed by various institutions will be considered for calibration of all other assays (Carter, 2011).

In the absence of a universal reference standard for in-house calibration, it is possible for clinical laboratories offering vitamin D testing services to assure good-quality performance by participating in an External Quality Assessment Scheme (EQAS). There are several programs evaluating 25-OHD measurement. The Vitamin D External Quality Assessment Scheme (DEQAS) is the only international specialist EQAS and includes assessment of 1,25(OH)2D testing as well as 25-OHD. DEQAS conducts periodic surveys based on samples provided by participant laboratories and calculates each laboratory's deviation from a specially computed All-Laboratory Trimmed Mean (ALTM) for that set of submitted samples. The ALTM serves as a consensus mean across different laboratories and different types of assays. In 1994, the ALTM showed good accuracy in comparison with GC-MS as a reference standard. DEQAS has found that most of the major methods yield results within 10% of the ALTM. DEQAS has plans to confirm the continuing validity of the ALTM approach by making a comparison with GC-MS once again since the mix of tests commonly used by laboratories has changed over time. It is imperative that clinical laboratories that sell vitamin D testing services participate in the DEQAS program or some other EQAS (Carter, 2011).

In addition to the question of accurate detection of the 25-OHD analyte, there are problems regarding the comparability of vitamin D testing results. The reference ranges reported by different laboratories are typically based on the 95% percentile range (mean ± 2 standard deviations) for a local population tested with the laboratory's particular test and materials. Not only do populations in different geographic regions exhibit varying mean vitamin D status, but it may not be appropriate to consider any population-based reference range as a "normal" range, given the widespread prevalence of vitamin D insufficiency according to Institute of Medicine (IOM) standards. The median-, upper-, and lower-limit values of such reference ranges do not necessarily correspond to the cutoff values established by the IOM or by other expert assessments (see **Testing and Monitoring**, *Optimum Serum 25-OHD Levels*). It would be more meaningful for a clinician to simply compare a patient's 25-OHD concentration with a recognized cutoff value (Kennel et al., 2010; Aloia, 2011; Carter, 2011). A factor that further complicates the interpretation of historical data is that assays may undergo modifications over time. The Centers for Disease Control and Prevention (CDC) has had to make adjustments to allow comparison of vitamin D insufficiency data collected from the National Health and Nutrition Examination Survey (NHANES) III (1988-1994) and NHANES 2003-2006 because of reagent and calibration lot changes in the DiaSorin RIA kit (NCHC, 2010).

REVIEW OBJECTIVES

PICO (Population/Intervention/Comparator/Outcome) Statement

The scope of this report is defined by the following PICO statement:

Population:

Healthy populations: Generally healthy adults, including pregnant women, and children without symptoms or findings of the outcome of interest.

Populations with known disease that may be linked with but does not cause vitamin D insufficiency: Adults and children with chronic diseases such as poor bone health, obesity, cardiovascular disease (CVD) (e.g., hypertension, heart failure, coronary artery disease), cancer, diabetes, multiple sclerosis (MS), or depression.

Intervention: Serum vitamin D testing

Comparator: No testing

Outcome:

Healthy populations: Growth, obesity, bone health and fractures or falls; all-cause mortality; and the incidence of other chronic diseases such as of CVD, cancer, diabetes, MS, and depression, as well as related mortality.

Populations with known disease that may be linked with but does not cause vitamin D insufficiency: Health outcomes related to the indication disease.

NOTE: *Healthy*, as used here, refers to absence of a disease known to cause vitamin D insufficiency, such as chronic kidney disease (CKD), and absence of the types of chronic disease for which vitamin D has been thought to create a risk. Study populations that were unselected on the basis of disease were considered healthy populations.

Analytic Framework

The causal pathway between vitamin D testing or screening and health outcomes, which is depicted in Figure 1, is complex. The most important question is represented by Arrow 6 in the figure: Does screening for low serum vitamin D levels or testing in individuals with evidence of low serum vitamin D improve health outcomes? If there is no evidence from studies designed to directly answer this question, other relevant questions include whether screening/testing results in increased intake of vitamin D (Arrow 2) and whether increased intake improves outcomes

by increasing serum levels (Arrows 3 and 4). (The role of sunlight exposure was not included in the framework because of the harms associated with ultraviolet light [UV] exposure, the inadequacy of sunlight during parts of the year at latitudes higher than 35°N, and the fact that the Institute of Medicine's [IOM's] current intake recommendations assume inadequate sunlight exposure.) Evidence that increased dietary intake or supplementation improves health outcomes would suggest the *potential* effectiveness of vitamin D screening/testing.

Material presented in the **BACKGROUND** and **TECHNOLOGY DESCRIPTION** sections of this report answers some of the questions presented in the analytic framework. While there is no gold standard against which to assess the accuracy of serum assays (Arrow 1), laboratories participating in quality assessment programs can assure that their methods produce results reasonably consistent with those of other participating laboratories. Regarding Arrow 3, an analysis of 26 randomized placebo-controlled trials has shown that that serum 25-OHD levels in healthy adults and in children rise with vitamin D supplementation, with or without calcium, and that the magnitude of improvement increases with dosage and duration of supplementation (Chung et al., 2009). The Key Questions of this report relate to Arrows 2, 4, 5, 6, and 7 of the analytic framework.

Arrow 1: Do available vitamin D assays accurately measure serum vitamin D (analytic validity)?

Arrow 2: Does vitamin D testing result in increased intake through an impact on patient behavior or clinical decision making?

Arrow 3: Does increased intake improve serum levels?

Arrow 4: Has a relationship between serum vitamin D levels and health outcomes been demonstrated and have clinically valid cutoff points for serum vitamin D measurement been defined (clinical validity)?

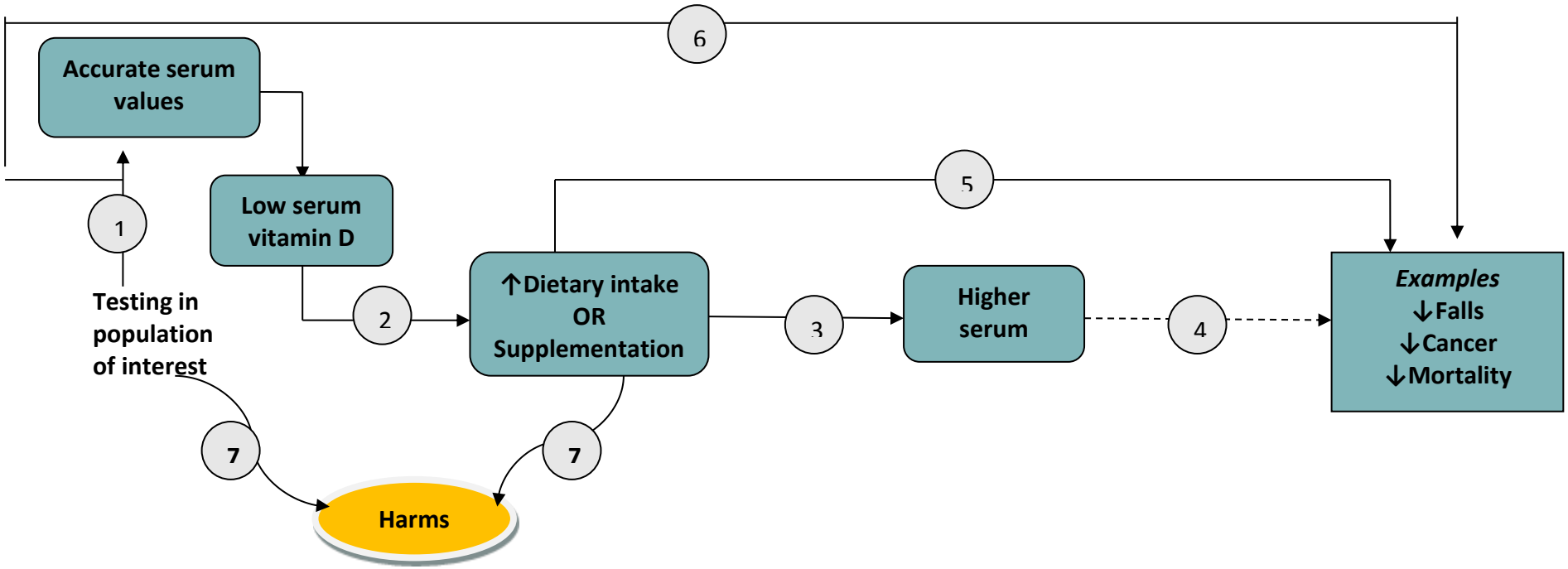
Arrow 5: Does increased intake improve health outcomes?

Arrow 6: Does screening for low serum vitamin D levels or testing in individuals with evidence of low serum vitamin D improve health outcomes?

Arrow 7: Are there harms associated with vitamin D testing or with subsequent supplementation?

NOTE: ***Bolded items are addressed by the Key Questions of this report. Other items are addressed in the*** **BACKGROUND** ***and*** **TECHNOLOGY DESCRIPTION** ***sections.***

Figure 1. Analytic Framework



Key Questions

The following key questions will be addressed:

1. Has a relationship between serum vitamin D and health outcomes been demonstrated and have clinically valid cutoff points for serum vitamin D measurement been defined (*clinical validity*)?

    a. In healthy populations
    b. In patients with chronic disease

2. Is there evidence that testing for serum vitamin D levels improves health outcomes (*clinical utility*)?

    a. As a routine screening test in healthy patients
    b. In patients who already have chronic disease thought to be associated with low serum vitamin D

3. Are there harms associated with vitamin D testing or with subsequent supplementation?

4. What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in (a) healthy populations and (b) populations who already have chronic disease, according to factors such as:

    <u>Patient characteristics</u>
    i. Age or life stage
    ii. Race or ethnicity
    iii. Geographic location
    iv. Nutritional status, diet, or personal use of calcium/vitamin D supplements
    v. Lifestyle factors such as smoking
    vi. Obesity
    vii. Baseline serum vitamin D level
    viii. Baseline risk of the health outcome of interest

    <u>Testing parameters</u>
    ix. Assay used
    x. Frequency of monitoring
    xi. Time of year

5. What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?

METHODS

Search Strategy and Selection Criteria for Key Question #1

There is a large volume of clinical literature on vitamin D and, as shown in Figure 1, a number of ways in which vitamin D status may be related to health outcomes. We focused our analysis on Key Questions #2 through #4, which relate to the clinical utility of vitamin D screening and testing. For Key Question #1, which relates to the clinical validity of test results, representative evidence was summarized in a descriptive manner. For each of the populations and general disease outcomes identified in the PICO statement, one or two recent systematic reviews, narrative reviews, or recent trials covering the associations of interest were selected. Selection took these considerations into account:

- Systematic reviews preferred over narrative review or individual trials
- Comprehensiveness and patient centeredness of outcomes
- Recency of review publication, or recency of studies included in reviews

In the Findings sections pertaining to Key Question #1, information and findings from the selected publications are summarized, but no critical appraisal is offered, and no evidence tables have been created.

Search Strategy and Selection Criteria for Key Questions #2, #3, and #4

Several systematic attempts were made to identify clinical trials designed to measure the direct effect of vitamin D screening/testing on patient outcomes (Arrow 6 in Figure 1) and the effect of screening/testing on increased intake (Arrow 2) through changes in patient behavior or clinical management decisions. These searches failed to identify any studies. Nor was this type of evidence discussed in recent systematic reviews, narrative review articles, or practice guidelines. Therefore, the Washington HTA Program chose to assess the impact of increased intake (supplementation) on patient outcomes (Arrow 5) as an indicator of the *potential* utility of screening/testing. *Screening or testing would not improve health outcomes if there were no effective treatment that could be recommended for individuals with low serum vitamin D.* Evidence considered for Key Question #2 addresses the issue of whether supplementation is an effective treatment and potentially identifies populations in which screening or testing might be effective. Evidence considered for Key Question #4 comes from the same trials selected for Key Question #2 but addresses the issue of whether the effectiveness of supplementation varies according to patient characteristics. If supplementation is only effective in individuals who are at high risk of vitamin D insufficiency because of factors such as age or race or who have high baseline risk of the outcome of interest, such findings would further define the subpopulations in which screening or testing might be effective. If the effect of supplementation differs according to baseline serum levels, then there is a clinical reason to test serum levels to assess the need for supplementation.
Randomized controlled trials (RCTs) and systematic reviews of RCTs evaluating vitamin D supplementation were eligible for selection to answer Key Questions #2 through #4. The following describes the pragmatic approach we took to searching for and selecting systematic reviews and RCTs. See Appendix I for additional detail.

Sources of Evidence for Healthy Populations and Musculoskeletal Health

The literature showed that the effect of supplementation on musculoskeletal health has been more extensively studied than any other set of outcomes. Multiple recent comprehensive systematic reviews, several of which have served to inform U.S. public health policy, have adequately addressed this general issue for healthy populations. Furthermore, the link between vitamin D status and bone health has been more clearly established than for other health outcomes. Therefore, systematic reviews were selected as evidence of the effect of supplementation on musculoskeletal health.

Sources of Evidence for Healthy Populations and Nonskeletal Health

RCTs published as of April 2009 were identified from a published systematic review of vitamin D and calcium for health outcomes in healthy populations, funded by the Agency for Healthcare Research and Quality (AHRQ) (Chung et al., 2009). Additional primary studies were identified through a literature search spanning April 2009 to April 2012. An update search for primary studies was conducted on July 31, 2012. Other searches were conducted to identify RCTs in populations that appeared to be missing from the review by Chung et al.

Sources of Evidence for Populations with Disease

For each of the disease populations identified in the PICO statement, the most recent and best-quality one or two systematic reviews, if available, were considered. We searched through April 2012 for RCTs that were published after the end of the review authors' searches or that addressed populations/outcomes not addressed in the systematic reviews. We also consulted the Excluded Studies list in the 2009 AHRQ report (Chung et al., 2009) for RCTs that were omitted because they did not meet that report's criterion requiring that ≤ 20% of study populations have chronic disease.

Excluded Indications

The literature reflects several populations and disease outcomes that were not named in the PICO statement, either because these populations/outcomes were not identified in topic scoping searches or because they were not considered critical to policymaking needs for the Washington State. A brief description of the type of evidence available for these additional populations and outcomes is described at the end of the Literature Review (**Evidence Pertaining to Indications Outside the PICO Statement**), but this evidence was not critically appraised and does not contribute to conclusions.

General Inclusion Criteria

- RCTs and systematic reviews of RCTs.
- Evaluation of the effect of vitamin D supplementation (or dietary changes designed to provide a certain dosage of vitamin D) on clinical outcomes.
- Generally healthy populations or populations defined by the presence of chronic disease listed in the PICO statement.
- Placebo, calcium-only, or (if the intervention was vitamin D plus calcium) calcium-plus-placebo control group.

General Exclusion Criteria

- Sample size < 20.
- Populations who have CKD, a history of bariatric surgery, some type of metabolic or malabsorption disorder, or any treatment that causes vitamin D depletion.
- Supplementation to treat disease complications, e.g., poor bone health in patients with HIV, or to correct treatment-related effects on bone health.
- Studies looking only at the effect of supplementation on serum levels.
- Treatment duration < 3 months (not applied to assessment of blood pressure changes in populations with hypertension).
- In generally *healthy* populations, most intermediate or physiological outcomes.
- Studies of topical vitamin D supplementation.

Specific Inclusion Criteria, Healthy Populations

In populations who were generally without the disease of interest, analyses of intermediate outcomes were excluded, with a few exceptions as noted in the following explanations. Health outcomes related to obesity included body mass index (BMI) and weight. Health outcomes related to musculoskeletal health included bone mineral content (BMC), bone mineral density (BMD), physical performance, falls, and fractures. Health outcomes related to CVD included hypertension, congestive heart disease, coronary artery disease, and cardiac events. Health outcomes related to cancer included survival and disease progression. Health outcomes related to diabetes included serum HbA1C, fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) results, or diagnosis of diabetes. No MS-related outcomes other than a diagnosis of MS were considered. Diagnosis of or symptoms of depression or any other mood disorder were considered.

Specific Inclusion Criteria, Disease Populations

In studies of populations already diagnosed with a chronic disease, any measure of disease activity or progression, disease-related complications, and functional outcomes were considered.

Search Strategy for Economic Evaluations and Practice Guidelines

The National Health Service Economic Evaluation Database (NHSEED) and MEDLINE were searched for economic evaluations. Practice guidelines were identified through searches of MEDLINE, systematic review databases, the National Guidelines Clearinghouse, and relevant professional associations. See Appendix I for additional detail.

Quality Assessment

Appendix II outlines the process of quality assessment used by Hayes for assessing the quality of primary studies and bodies of evidence. Internally developed Quality Checklists for individual studies address study design, integrity of execution, completeness of reporting, and the appropriateness of the data analysis approach. Individual studies are labeled as *Good, Fair, Poor, or Very Poor*. The Evidence-Grading Guides assure that assessment of bodies of evidence takes into account not only methodological quality in individual studies but also the applicability of bodies of evidence to the population(s), intervention(s), and health outcome(s) of interest; the consistency of results across studies; and the quantity of data (number of studies and sample sizes). The quality of bodies of evidence for particular outcomes are labeled as *High, Moderate, Low, or Very Low*. These labels can be interpreted in the following manner:

High: Suggests we can have high confidence that the evidence found is reliable, reflecting the true effect, and is very unlikely to change with the publication of future studies.

Moderate: Suggests we can have reasonable confidence that the results represent the true direction of the effect but that the effect estimate might well change with the publication of new studies.

Low: We have very little confidence in the results obtained. Often occurs when the quality of the studies is poor, the results are mixed, and/or there are few available studies. Future studies are likely to change the estimates and maybe even the direction of the results.

Very low: Suggests no confidence in any result found. Often occurs when there is a paucity of data or the data are such that we cannot make a statement on the findings.

Overall bodies of evidence are assessed according to the quality of the lowest-quality body of evidence for a key outcome.

For this report, quality labels were not assigned to the selected systematic reviews. Rather, the following considerations determined the selection of systematic reviews and the manner in which they were used:

1. Given its objectives and search strategy description, can this systematic review be used to identify a certain set of studies in the place of a literature search?

2. Does the systematic review provide sufficient individual study data to allow a judgment about review conclusions?

3. Are the data summarized or pooled in a way that answers the key questions of the Washington State evidence report?

4. Does the systematic review provide sufficient information about the quality of individual studies to allow a judgment of the quality of the body of evidence?

When systematic reviews were used for purposes other than to simply identify primary studies, the review authors' assessment of study quality, if adequately described, was taken into account when assessing the quality of bodies of evidence.

The Appraisal of Guidelines Research and Evaluation (AGREE) (AGREE Enterprise, 2012) tool was used to assess the quality of practice guidelines.

Special Considerations

Given the long time frames of many studies and the unlikely expectation on the part of clinicians and investigators that treatment assignment would have a dramatic or immediate benefit to patients; inadequate allocation concealment was not considered a serious study limitation in the studies evaluating outcomes in healthy populations. Where outcomes were objective, such as measurement of blood pressure, diagnosis of cancer, or mortality/survival, lack of blinding was not considered an important study limitation. Adherence to prescribed supplementation regimens and protocol allowance

of continued personal supplementation were also not taken into account for evaluating individual study quality since the primary interest of this report is the real-world effectiveness of vitamin D testing and subsequent treatment rather than the efficacy of supplementation.

For purposes of assessing the applicability of bodies of evidence, we assumed that vitamin D supplementation at the doses currently recommended by the Institute of Medicine (IOM) was the specific intervention of interest, although this was not specified in the PICO statement.

LITERATURE REVIEW

Search Results

Search result details are presented in the discussion of Findings for each Key Question. Overall results can be summarized as follows:

Key Question #1: 13 systematic reviews, 6 narrative reviews, 3 observational studies

Key Questions #2 to #4: 10 systematic reviews, 41 randomized controlled trials (RCTs) or trial reports

Key Question #5: 1 cost analysis, 3 cost-effectiveness studies

Practice Guidelines and Public Health Policies: 26 documents reviewed, of which 17 had recommendations pertinent to this report

Excluded Studies

Several studies were excluded for reasons other than the prespecified inclusion/exclusion criteria. These are listed in Appendix VII.

Key Questions and Findings

Key Question #1a: Has a relationship between serum vitamin D and health outcomes been demonstrated *in healthy populations* and have clinically valid cutoff points for serum measurement been defined (clinical validity)?

Findings

The following discussion draws heavily on the findings of a series of four evidence reports produced by the Agency for Healthcare Research and Quality (AHRQ). For the discussion of Findings pertaining to Key Question #1, these reports are referred to as the *2007 AHRQ report* (Cranney et al., 2007; bone health), *2009 AHRQ report* (Chung et al., 2009; bone and other health outcomes), *2010 AHRQ report* (Pittas et al., 2010; cardiometabolic outcomes), and *2011 AHRQ report* (Chung et al., 2011; cancer and fractures). Citations have been omitted for easier reading. Given the comprehensiveness of these reports and their use by the Institute of Medicine (IOM) and the U.S. Preventive Services Task Force (USPSTF), these publications were consulted first for answers to Key Question #1a. Other representative systematic reviews and narrative reviews were consulted for an overview of evidence pertaining to outcomes that

were not addressed in the AHRQ reports. The data reported by the AHRQ reports came from prospective cohort studies and nested case-control studies, which represent study designs least subject to bias in assessing epidemiological associations. In the AHRQ reports, control for confounders was one of the factors that contributed to study quality assessments. Other systematic review authors acknowledged that individual studies generally controlled for confounders but the studies varied as to which confounders were considered.

Obesity

No observational studies measuring the association between vitamin D and the presence or risk of obesity were identified by the second AHRQ report, which addressed a range of various health outcomes, although *obesity* was covered in the report's search strategy. No review articles providing such data were identified in the search conducted for the current report. An RCT that compared the effects of two hypocaloric diets in overweight or obese women found that the diet associated with greater weight loss also led to greater vitamin D intake and a greater mean increase in serum 25-hydroxyvitamin D (25-OHD) levels (Ortega et al., 2009). No conclusions about causality can be drawn from this study.

Musculoskeletal Health

Adults: The 2007 AHRQ report found a positive association of serum 25-OHD with higher bone mineral density (BMD) or increase in BMD at the femoral neck in postmenopausal women and elderly men, with thresholds ranging from 30 to 80 nanomoles per liter (nmol/L); the evidence was judged to be of fair quality. Collectively, the AHRQ reports found inconsistent evidence pertaining to an association with physical performance measures, fractures, and falls, and available studies of these outcomes were restricted to postmenopausal women and older men. Infants and Young Children: The 2007 AHRQ report found inconsistent evidence regarding an association of serum 25-OHD with BMD in infants but fair-quality evidence of an inverse association between serum 25-OHD levels and established rickets in infants and children. Older Children and Adolescents: The 2007 AHRQ report found a positive association between serum 25-OHD and both baseline BMD and change in BMD in older children (fair-quality evidence). Pregnant and Lactating Women: The 2007 AHRQ report concluded that there was insufficient evidence pertaining to a relationship between serum 25-OHD and change in BMD during pregnancy.

Cancer (Adults)

The 2011 AHRQ report described findings from 3 fair- to good-quality cohort studies suggesting a positive (harmful) association of high levels of vitamin D with cancer mortality in men, but a statistically significant trend was detected in only 1 study. Only one study provided data regarding association with cancer mortality in women; no overall association was observed. For specific cancer types, authors of the 2011 AHRQ report calculated pooled odds ratios (ORs) for risk of cancer per 10 nmol/L increase in serum 25-OHD, with adjustment for as many potential confounders as possible. An inverse (protective) association was found between high vitamin D levels and reduced risk of colorectal cancer (CRC), but no association was found for prostate cancer or breast cancer. Similarly, a more recent meta-analysis observed a significant inverse association between increases of 100 international units per liter (IU/L) in serum 25-OHD and reduced risk of CRC (Touvier et al., 2011). The 2009 AHRQ report described mixed findings for pancreatic cancer, with the results seemingly related to cutoff value and ultraviolet (UV) light exposure area. An independent group of researchers also found no association between 10

nanograms per milliliter (ng/mL) (25 nmol/L) increase in serum 25-OHD and prostate cancer overall or aggressive prostate cancer (Gilbert et al., 2011). On the other hand, a meta-analysis that fit data to a variety of functions (linear, quadratic, exponential, power, and logarithmic) came to somewhat different conclusions from those of the 2009 AHRQ report with regard to breast cancer (Grant, 2010). Grant determined that the adjusted data from selected studies were best fit by nonlinear functions and that a 50% reduction in the incidence of breast cancer was associated with a level of 78 nmol/L, compared with 24 nmol/L as the reference. (Grant also estimated a 50% reduction in CRC, comparing 60 nmol/L with 15 nmol/L 25-OHD, which is consistent with the AHRQ findings). Another recent meta-analysis of 10 prospective cohort studies and nested case-control studies suggested that baseline serum 25-OHD could be protective against ovarian cancer, although the results were not statistically significant (relative risk [RR], 0.83; 95% confidence interval [CI], 0.63 to 1.08 for every 20 ng/mL [50 nmol/L] increase) (Yin et al., 2011a). Using data from 8 studies, the same researchers found a significant 0.82 OR for incident colorectal adenoma (considered a risk factor for CRC) for every 20 ng/mL increase in serum 25-OHD (Yin et al., 2011b).

Cardiovascular Disease (Adults)

The 2009 AHRQ report concluded that there is an inverse association between baseline serum 25-OHD (cutoff, 37.5 nmol/L) and the incidence of cardiovascular events at follow-up intervals of 5.4 to 10 years; this evidence came from two studies considered to be of good quality. The 2010 AHRQ report described mixed findings from 9 generally good prospective cohort studies regarding an association with cardiovascular events: no association in 4 studies, and an inverse association in 5 studies. In the 2010 AHRQ report, 2 of 3 included studies that evaluated fatal cardiovascular events found an inverse association, and 2 studies that evaluated myocardial infarction (MI) reported conflicting results. Two fair-quality studies included in the 2009 report suggested an inverse (protective) association between serum 25-OHD and the incidence of hypertension over 4- and 8-year follow-up intervals, while the 2010 report expanded on this finding with a meta-analysis of 3 studies, comparing 25-OHD levels < 37.5 to 50 nmol/L with levels ≥ 75 to 81 nmol/L; the results showed an inverse (protective) relationship (RR, 1.76; 95% CI, 1.27 to 2.44). Considering cardiometabolic outcomes in general (hypertension, cardiovascular events, and outcomes related to diabetes), the 2010 AHRQ report observed that 25-OHD levels of 62 to 87 nmol/L were associated with lower disease risk, using levels at 25 To 37 nmol/L as the reference.

Type 2 Diabetes

Adults: The AHRQ reports did not evaluate vitamin D and type 2 diabetes. A recent systematic review combined data from 4 longitudinal studies and found that a serum concentration > 25 ng/mL (62.5 nmol/L), compared with a concentration < 14 ng/mL (35 nmol/L), was associated with a statistically significant 43% reduction in the incidence of type 2 diabetes at 1.3 to 22 years (Mitri et al., 2011a).
Pregnant and Lactating Women: A systematic review and meta-analysis of 7 cross-sectional or case-control studies found that serum 25-OHD < 50 nmol/L was significantly associated with gestational diabetes (Poel et al., 2012). Cross-sectional and non-nested case-control studies do not allow an assessment of causality because the link between exposure (vitamin D status) and disease can be in either direction or both findings can be the result of a third factor.

Multiple Sclerosis (and Other Autoimmune Disorders)

No studies of serum 25-OHD and risk of MS met the inclusion criteria of cohort study or nested case-control study for the relevant AHRQ report (Chung et al., 2009). According to a recent narrative review

(Pierrot-Deseilligny, 2009), only 1 study has evaluated the association between serum level 25-OHD and incident multiple sclerosis (MS). The authors describe the study as a methodologically sound case-control analysis (257 cases occurring among young American soldiers, 514 controls). Within the subgroup of white soldiers, MS was significantly associated with a serum level of 15 to 63 nmol/L compared with a serum level of 99 to 152 nmol/L (P<0.01). The relationship was not significant in the smaller subgroup of black American soldiers, who had, on average, lower serum levels. Another review article (Zhang and Wu, 2010) cited a different study in which MS patients, compared with controls, had lower levels of serum vitamin D. These case-control studies were not reported to be nested case-control studies (derived from larger longitudinal studies) and thus are poor assessments of causality.

Research has also suggested an association between vitamin D status and diseases such as systemic lupus erythematosus, rheumatoid arthritis, polymyositis/dermatomyositis, inflammatory bowel disease, and systemic scleroderma (Hyppönen, 2010; Marques et al., 2010; Pelajo et al., 2010). These particular autoimmune disorders were not specified in the PICO (Population/Intervention/Comparator/Outcome) statement (see **METHODS**) and were not addressed for Key Questions #2 to #5.

Mood Disorders

The AHRQ reports did not evaluate mood disorders. Three narrative, or possibly systematic, review articles were consistent in reporting that cross-sectional and case-control studies suggest a link between lower vitamin D levels and depression, seasonal affective disorder (SAD), or premenstrual syndrome (PMS) (Murphy and Wagner, 2008; Bertone-Johnson, 2009; Parker and Brotchie, 2011). As Bertone-Johnson points out, these observations would be consistent with low vitamin D as the cause of depression, low vitamin D as an indirect consequence of depression, or vitamin D and depression as simultaneous consequences of another factor. No review articles cited longitudinal studies, which would provide greater support for a causal theory.

All-Cause Mortality

The 2009 AHRQ report found mixed study results with regard to the association between baseline serum 25-OHD and all-cause mortality at 27 to 104 months, but the best-quality study suggested an inverse (protective) association. A more recent systematic review, with meta-analysis, calculated an RR of 0.71 (95% CI, 0.50 to 0.91), comparing highest with lowest 25-OHD levels in 11 studies (59,231 participants) (Zittermann et al., 2012). In further calculations using 27.5 nmol/L as a reference value, increasingly high serum concentrations were associated with increasing risk reduction with incremental benefit subsiding somewhere between 77.5 and 115 nmol/L. Zittermann and colleagues did not apply any selection criteria related to study population characteristics. Additionally, a recently published cohort study that followed 1018 older adults for 11 years found a protective association between serum 25-OHD concentrations and a composite outcome of incident hip fracture, MI, or death (de Boer et al., 2012). Optimal, season-specific cutoff values ranged from 43 nmol/L (winter) to 61 nmol/L (summer).
Nonskeletal Outcomes Related to Pregnancy or Lactation

Gestational vitamin D deficiency has been linked not only with low birth weight and fetal bone mineral content (BMC), but also with preterm labor, preterm birth, infections, and severe eclampsia (Bell, 2011).

Summary, Clinical Validity of Serum 25-OHD in Healthy Populations (Key Question #1a)

A noncritical review of recent systematic reviews, narrative reviews, and clinical trials supports the following description of what is known about the link between serum levels of vitamin D and the risk of disease.

Evidence suggests a harmful association of serum 25-OHD with:

Cancer mortality in men

Evidence suggests a protective association of serum 25-OHD with:

Bone health
Cardiovascular health
Type 2 diabetes
Colorectal cancer
Ovarian cancer
All-cause mortality

Regarding a link with bone health, fair-quality (according to key systematic reviews) evidence has shown a link with BMD in some populations, but evidence to date has not shown a link with outcomes such as fracture or falls, and recent systematic reviews suggest that no studies have investigated a link with any measure of bone health in younger adults. Analyses by assay were missing in the reviewed literature.

Unclear link (mixed results) of serum 25-OHD with risk of:

Cancer other than CRC or ovarian cancer

The results as reported in the literature reviewed for this report were inconsistent.

Insufficient evidence regarding association of serum 25-OHD:

Obesity
Gestational diabetes
MS
Depression and mood disorders

Evidence regarding a link with risk of obesity, gestational diabetes, MS, and mood disorders is missing, sparse, or based on lower-quality study designs that are subject to bias (non-nested case-control studies) or ecological fallacy (cross-sectional studies). The selected literature did not provide data for pediatric populations.

Cutoff values

For disease outcomes where a link has been demonstrated, the evidence does not support definitive cutoff points at which 25-OHD serum levels can be expected to predict optimal overall health. Some studies have conducted analyses according to different strata of serum levels and studies have varied as to how those strata are defined. Other studies have analyzed associations treating serum level as a continuous variable without specifying a cutpoint. Furthermore, optimal thresholds may vary by the outcome of interest. However, evidence to date is consistent with approximately 30 nmol/L as the level

below which there is a risk of deficiency and a threshold ≥ 50 nmol/L, and possibly as high as 70 nmol/L, for optimal health.

Implications for vitamin D screening

Screening for low vitamin D levels in healthy populations could serve to provide a general health indicator, given the association with several forms of chronic disease and with all-cause mortality. However, the lack of definitive cutoff points diminishes the validity of serum measurements and thereby sheds doubt on the utility of vitamin D screening, and findings of a possible harmful association between serum 25-OHD and cancer mortality in men complicates interpretation of serum measurements.

Key Question #1b: Has a relationship between serum vitamin D and health outcomes been demonstrated in populations with *chronic disease* and have clinically valid cutoff points for serum measurement been defined (clinical validity)?

Findings

Obesity

Cross-sectional analysis of 441 obese individuals showed that individuals with serum 25-OHD < 40 nmol/L, compared with individuals with levels ≥ 40 nmol/L, had significantly higher depression scores (Jorde et al., 2008).

Musculoskeletal Health

Available systematic reviews exploring the association between serum 25-OHD and bone health measures did not generally differentiate between populations with and without evidence of poor bone health.

Cancer

A systematic review identified 8 cohort or case-control studies that evaluated the prognostic value of low vitamin D status in patients with cancer, considering overall survival, cancer-free survival, progression-free survival, and/or event-free survival as outcomes (Buttigliero et al., 2011). Only 1 or 2 studies were available per cancer type. They suggested that lower serum 25-OHD is associated with a better prognosis in patients with colon cancer, prostate cancer, or melanoma but no association between serum 25-OHD and outcomes in non–small-cell lung cancer was observed. Two studies of breast cancer patients reported conflicting results, with one study showing no association and the other suggesting a protective effect starting at 32 ng/mL, but a harmful effect at levels > 44 ng/mL. A prospective cohort study published after the systematic review by Buttigliero and colleagues reported inconclusive findings regarding the relationship between serum 25-OHD and breast cancer recurrence (Jacobs et al., 2011). With ≥ 30 ng/mL as a reference, ORs for three levels of low 25-OHD concentrations (< 10 ng/mL, 10 to 20 ng/mL, and 20 to 30 ng/mL) were approximately null (1.00 to 1.14), but wide CIs included values consistent with both a protective effect from *low* vitamin D status (lower bounds, 0.57 to 0.76) and a harmful effect from low vitamin D status (upper bounds, 1.47 to 2.31). No significant associations were observed in subgroups defined by menopausal status, cancer stage, or ultimate

survival. A meta-analyses of data from 2 studies has suggested the possibility of a protective effect of serum 25-OHD against recurrent colorectal adenoma (OR, 0.87; 95% CI, 0.56 to 1.35) (Yin et al., 2011b).

Cardiovascular Disease

A prospective cohort study described in the AHRQ report by Pittas et al. (2010) reported that the association between lower serum 25-OHD and overall cardiovascular events was significant only in participants with hypertension at baseline.

Type 2 Diabetes

A systematic review of vitamin D and hyperglycemia (Thomas et al., 2012) described a small cohort study (n=289) in which diabetic patients with serum 25-OHD < 13.9 nmol/L (bottom decile) had a 96% (95% CI, 20% to 213%) increased risk of all-cause mortality over a median follow-up of 15 years. In a cross-sectional analysis of data for 1216 adults who participated in the 2001 to 2006 National Health and Nutrition Examination Survey (NHANES) and who had diagnosed diabetes, individuals with nephropathy were more likely than individuals without nephropathy to have vitamin D deficiency (Diaz et al., 2009). In a logistic regression model adjusting for a wide range of confounders, vitamin D *deficiency* was associated with increased odds of nephropathy (OR, 1.85; 95% CI, 1.06 to 0.23), as was vitamin D *insufficiency* (OR, 1.79; 95% CI, 1.12 to 2.85).

Multiple Sclerosis

Pierrot-Deseilligny (2009) cites studies suggesting that MS patients have lower serum levels during relapse than at other times.

Mood Disorders

A narrative review cites a study that reported an inverse association between vitamin D levels and depression severity in patients with a diagnosis of depression (Bell, 2011).

Summary, Clinical Validity of Serum 25-OHD in Populations with Chronic Disease (Key Question #1b)

In the literature reviewed for this report, there was very sparse evidence concerning an association between serum levels of 25-OHD and disease-related outcomes in individuals with chronic disease. A very small quantity of data suggests that higher levels of serum 25-OHD may be associated with better prognosis for some types of cancer (colon, prostate, and melanoma; longitudinal data), fewer cardiovascular events in individuals with hypertension (longitudinal data), fewer complications in individuals with diabetes (longitudinal and cross-sectional data), fewer relapses in individuals with MS (cross-sectional data), and less severe symptoms in individuals with depression (cross-sectional data). Cutoff points have not been established. The literature reviewed did not provide data for pediatric populations defined by disease presence.

Implications for vitamin D screening

Vitamin D screening may have promise for establishing a prognosis in patients with colon cancer, prostate cancer, or melanoma, and for assessing the risk of disease-related events and complications in

patients with hypertension and diabetes. However, the evidence is too sparse to support clinical rules or cutoff points.

Key Question #2a: Is there evidence that testing for serum vitamin D levels as a routine screening test in *healthy* populations improves health outcomes (clinical utility)?

As noted in the **METHODS** section of this report, the literature does not provide direct evidence of the effectiveness of vitamin D screening. Six systematic reviews and 14 RCTs (23 publications) evaluating the effect of vitamin D supplementation on the health outcomes of interest were identified; details are provided in Appendixes III and IV. It is noteworthy that study participants were not selected on the basis of vitamin D test results.

One of the selected RCTs was the Women's Health Initiative (WHI), a 7-year U.S. study following 36,282 postmenopausal women, all of whom were age 50 years or older. Women were randomized to 400 IU/day of vitamin D plus calcium, or to placebo, and were allowed continued use of personal supplements. Baseline serum 25-OHD levels were not reported for the overall study group. However, in a nested case-control analysis derived from this study, 72% of women had baseline serum levels < 52.4 nmol/L (LaCroix et al., 2008). According to national survey data, the prevalence of vitamin D insufficiency (< 50 nmol/L) in American women ≥ 50 years of age is approximately 28% (Looker et al., 2011). Thus, compared with the overall American population, the WHI trial population had a much greater prevalence of vitamin D insufficiency. Nine different publications provided data from this trial that were pertinent to Key Question #2a.

Findings

Musculoskeletal Health

Evidence pertaining to musculoskeletal health was obtained from 6 systematic reviews of RCTs (Cranney et al., 2007; Chung et al., 2009; Michael et al., 2010; Chung et al., 2011; Murad et al., 2011; Winzenberg et al., 2011). Given the recency of these reviews and the less controversial nature of a relationship between vitamin D and bone health, more recently published RCTs were not selected.

Adults, BMD, and Physical Performance: The 2007 AHRQ report (Cranney et al., 2007) concluded, based on > 7 RCTs and meta-analysis where possible, that vitamin D3 (≤ 800 IU/day) plus calcium resulted in small increases in BMD of the spine, total body, femoral neck, and total hip in populations consisting predominantly of women in late menopause. Three additional RCTs in older women reviewed in the 2009 AHRQ report (Chung et al., 2009) were consistent with this conclusion. Five RCTs included in the two reports resulted in inconsistent findings for an effect on physical performance measures.

Adults, Falls: Another systematic review with meta-analysis, also funded by the AHRQ, found that vitamin D at median doses of 800 IU, with or without calcium, reduced the incidence of falls (RR, 0.82; 95% CI, 0.77 to 0.89) in community-dwelling older adults (9 RCTs; 5780 participants) (Michael et al., 2010). A systematic review and meta-analysis commissioned by The Endocrine Society reported results very similar to those reported by Michael et al., although no restriction on participant dwelling was made: OR, 0.86 (95% CI, 0.77 to 0.96) for vitamin D with or without calcium, based on 26 RCTs and 45,782 participants with a mean age of 76 years (Murad et al., 2011). In the studies reviewed by Murad et al., patients generally received vitamin D at doses of 400 to 1000 IU/day. The population represented

by the studies included in the review by Murad et al. was at substantial risk of falls (median risk, 50%; range, 15% to 69% across studies). Statistical tests for interaction suggested that the treatment effect did not differ by community versus institutional dwelling.

Adults, Fractures: The 2011 AHRQ report (Chung et al., 2011) found that pooled data from 5 RCTs (14,583 participants) suggested no effect of vitamin D in studies in which vitamin D supplements were used *with or without* calcium on the incidence of fractures in elderly men or women; subgroup analysis of institutionalized and community-dwelling individuals produced similar results. However, a pooled RR of 0.88 (95% CI, 0.79 to 0.99), based on 11 RCTs (52,915 participants), was calculated for the effect of vitamin D *plus calcium*. Subgroup analysis suggested that vitamin D plus calcium is effective in both institutionalized individuals and community-dwelling individuals as well as overall.

Infants, Children, and Adolescents: Combined data from the 2007 (Cranney et al., 2007) and 2009 (Chung et al., 2009) AHRQ reports pertaining to an effect on BMC or BMD in infants, children, and adolescents were inconsistent across studies and studies with positive results showed only small effects. A more recent meta-analysis of 6 RCTs (total, n=1213) conducted in older children and adolescents found no statistically significant effects on forearm, hip, lumbar spine, or total body BMC/BMD, and pooled effect sizes were very small (Winzenberg et al., 2011).

Pregnant or Lactating Women: No relevant RCTs in this population were identified.

Summary: Nine RCTs conducted in postmenopausal or predominantly postmenopausal women were consistent in demonstrating a beneficial effect from vitamin D plus calcium on BMD. Evidence pertaining to an effect on physical performance was inconsistent. Evidence from 26 RCTs (45,782 participants) showed vitamin D supplementation to be effective in preventing falls in older adults (predominantly postmenopausal women), with subgroup analysis suggesting that calcium was necessary for vitamin D to be effective. Subgroup analysis in this systematic review, combined with another more focused systematic review that included 9 trials involving only community-dwelling older adults, also demonstrated that effectiveness does not differ by setting. Similarly, a systematic review showed that vitamin D plus calcium (11 RCTs; 52,915 participants) was effective in reducing fracture in elderly men or women, regardless of setting, but pooled data from 5 RCTs suggested no effect from vitamin D with or without calcium. Three systematic reviews have not been able to demonstrate a consistent effect on BMC or BMD from vitamin D alone or with calcium in infants, children, or adolescents.

The RCTs included in these various reviews were generally judged by the review authors to be of fair quality or to have satisfied most of the criteria defined by the authors for control of bias and adequate reporting. Many of the studies used supplementation dosages below current Institute of Medicine (IOM) recommendations, which may have led to an underestimation of benefit. Findings of no effect were often imprecise, based on estimates with somewhat wide CIs, due, in part, to few studies. The estimates of effect on fractures in the 2011 AHRQ report may be imprecise since only one type of fracture was selected from each study. The overall body of evidence pertaining to the effect of vitamin D on musculoskeletal health is of low quality.

Evidence not Reviewed in Detail: Two additional systematic reviews of trials assessing drug treatments for prevention of fractures came to our attention after the initial search for this report (Bischoff-Ferrari et al., 2012; Murad et al., 2012). These analyses were not reviewed in detail because conclusions were consistent with those of Chung et al. (2011). Murad et al. reported a significant pooled OR for the effect of vitamin D, or vitamin D analog, in combination with calcium on hip fracture (0.81; 95% CI, 0.68 to

0.96) (46,933 participants) but nonsignificant ORs of 0.96 to 1.13 for the effect of vitamin D analog plus calcium on vertebral (46,711 participants) and nonvertebral fracture (46,711 participants) as well as for the effect of vitamin D analog alone on hip fracture (12,469 participants), vertebral fracture (4235 participants), and nonvertebral fracture (235 participants). Bischoff-Ferrari et al. restricted study selection to double-blind RCTS involving patients ≥ 65 years of age, obtained patient-level data (31,022 participants) from 11 of 14 eligible trials, and using these data, calculated pooled estimates of risk reduction. They reported the following overall hazard ratios (HR): HR, 0.90 (95% CI, 0.80 to 1.01) for hip fracture and HR, 0.93 (95% CI, 0.87 to 0.99) for nonvertebral fracture. As in the previously described AHRQ reports, the available evidence for these newer systematic reviews remained applicable primarily to postmenopausal women.

Obesity

Three RCTs (Nilas and Christiansen, 1984, fair; Caan et al., 2007, good; Daly and Nowson, 2009, fair) evaluated the effect of vitamin D supplementation on body weight or development of obesity. Two trials (Nilas and Christiansen, 1984; Caan et al., 2007) enrolled only postmenopausal women. The smaller trial (n=238) conducted by Nilas and Christiansen detected no change in weight over a 1- or 2-year period in either the vitamin D (2000 IU/day) or placebo group. Nilas and Christiansen analyzed outcomes in a subgroup of overweight women and found no differences in outcome between vitamin D and placebo. The other study (Caan et al.), which was derived from the WHI trial, included 22,827 participants who were not obese at baseline; over a 7-year follow-up, slightly *less* weight gain was observed among the nonobese participants who were randomized to vitamin D, although the prescribed dose of vitamin D was relatively low (400 IU/day): –0.08 kilogram (kg) (CI, –0.23 to 0.06) for normal-weight individuals and –0.09 kg (95% CI, –0.22 to 0.04) for overweight individuals.

The third RCT enrolled Caucasian men (n=167) (Daly and Nowson, 2009). Participants were, on average, middle aged (mean age, 61 years) and mildly overweight (BMI, 26.2). Men randomized to the treatment group added fortified milk (400 IU/day of vitamin D3) to their diets. No effect on weight change over a 2-year period was observed, and, in fact, neither group exhibited meaningful weight changes.

Summary: One good-quality RCT (n=11,383) suggested that vitamin D may slightly retard weight gain over the long term in older women who are not obese. Two fair-quality studies using higher doses of vitamin D did not demonstrate an effect in middle-aged to older nonobese adults over a 1- to 2-year time frame. Baseline serum 25-OHD levels were reported only in one of the studies; findings in this study were negative and serum levels were relatively high (67 to 78 nmol/L in the control and intervention groups). Participants in the study with positive results were permitted to use additional personal supplementation, but use of nonstudy vitamin D in the other two trials was not clear. This body of evidence is of low quality due to heterogeneity in study protocols, inconsistent findings, and the small number of trials.

Cancer

Three RCTs (40,165 participants) reported in 7 publications evaluated cancer-related outcomes (Trivedi et al., 2003; Wactawski-Wende et al., 2006; Lappe et al., 2007; Chlebowski et al., 2008; Brunner et al., 2011; Tang et al., 2011). The following results were reported:

- No significant effect on cancer incidence or on cancer-related mortality over a follow-up period of 5 or 7 years (Trivedi et al., 2003; Wactawski-Wende et al., 2006), including CRC and related

mortality (Wactawski-Wende et al., 2006). RRs ranged from suggesting a somewhat protective effect to a slightly harmful effect and all were nonsignificant.

- A reduction in the incidence of any cancer over 4-year follow-up (RR, 0.402; 95% CI, 0.20 to 0.82; *P*=0.013) (Lappe et al., 2007).
- No significant effect on breast cancer incidence (HR, 0.96; 95% CI, 0.89 to 1.09), and equal breast cancer mortality in both groups over 7-year follow-up (Chlebowski et al., 2008).
- No significant effect on the incidence of either nonmelanoma skin cancer or melanoma over 7-year follow-up, but a trend toward a reduction in cancer mortality (HR, 0.9; 95% CI, 0.77 to 1.05) (Tang et al., 2011).
- No effect on the incidence of invasive cancer or related mortality over 7-year follow-up (HR, 0.98; 95% CI, 0.9 to 1.05) (Brunner et al., 2011).

Three of these studies were analyses derived from the WHI study (vitamin D at 400 IU/day plus calcium versus placebo) (Wactawski-Wende et al., 2006; Chlebowski et al., 2008; Brunner et al., 2011); however, the analysis by Chlebowski et al. pertained to a nested case-control group of 1792 evaluable participants. As in the WHI study, the participants in the study by Lappe et al. (2007) were postmenopausal women; the vitamin D group received 1000 IU/day, combined with calcium. The study by Trivedi et al. (2003) included older adults (age 65 to 85 years) who were not currently using supplements; vitamin D was administered *without* calcium at a dose of 100,000 IU every 4 months. Factors that might explain the positive results in the study by Lappe et al., while other studies reported negative results, would be a high baseline level of serum 25-OHD (mean, 72 nmol/L in the study by Lappe et al. versus 52 nmol/L in the study by Chlebowski et al.; baseline 25-OHD was not reported for the other studies) or, more likely, a higher dose of vitamin D (1000 IU/day compared with 400 IU/day or an equivalent of 800 IU/day in the other studies).

The 2011 AHRQ report (Chung et al., 2011) reviewed the RCTs by Trivedi et al. (2003), Wactawski-Wende et al. (2006), Lappe et al. (2007), and Chlebowski et al. (2008) and concluded that the evidence does not allow a determination of the benefit or harm of vitamin D supplementation for prevention of cancer.

Summary: The evidence is inconclusive regarding the effect of vitamin D supplementation on cancer outcomes in older adults. CIs surrounding several of the null findings were either wide and included values consistent with both benefit and harm, or suggested a protective effect by a lower bound at some distance from the null value and an upper bound close to the null. The 3 trials represented by this body of evidence varied with respect to whether and in what manner nonstudy vitamin D supplementation was allowed. The overall quality of the evidence for older adults is low due to inconsistency in the magnitude of estimates, nonsignificant estimates, variation in the target cancers, and varied treatment protocols. No evidence applicable to younger adults was identified. This conclusion is consistent with the pooled estimates and conclusion expressed by the 2011 AHRQ report (Chung et al., 2011).

Cardiovascular Disease

Three publications related to 2 RCTs (38,968 participants) evaluated CVD-related outcomes (Trivedi et al., 2003; Hsia et al., 2007; Margolis et al., 2008). Two of these studies were analyses derived from the WHI study, which randomized 36,282 postmenopausal women to daily supplementation with 400 IU vitamin D plus calcium or placebo (Hsia et al. 2007; Margolis et al. 2008). The study by Trivedi et al.

(2003) included 2686 older adults (age 65 to 85 years) who received 100,000 IU vitamin D or placebo every 4 months (approximately 833 IU/day). Baseline serum 25-OHD was not reported.

One of the WHI study analyses evaluated the effect of vitamin D supplementation on the development of hypertension and detected no effect (Margolis et al. 2008). (Another study, which did not meet inclusion criteria because only the intermediate outcome of blood pressure was assessed, showed no effect on blood pressure [Daly and Nowson, 2009]).

The other two selected study reports evaluated vitamin D supplementation for prevention of CVD events (Trivedi et al., 2003; Hsia et al., 2007). Trivedi et al. reported nonsignificant estimates favorable to vitamin D alone: an RR of 0.90 (95% CI, 0.77 to 1.06) for incidence of CVD and an RR of 0.84 (95% CI, 0.65 to 1.10) for CVD mortality. However, in the study by Hsia et al., vitamin D plus calcium had no overall effect on a composite measure of coronary artery disease (CAD) mortality or MI, or on the incidence of stroke, coronary revascularization, heart failure, angina, or transient ischemic attack (Hsia et al., 2007).

Summary: Three analyses of two large good-quality RCTs (38,968 participants) suggested that supplementation with relatively low-dose vitamin D plus calcium had no effect on the risk of hypertension or incidence of CVD events in postmenopausal women but that vitamin D alone at a dose consistent with IOM standards may have had a beneficial effect on CVD incidence and CVD-related mortality. Participants in the larger study, which reported negative results, were permitted to use additional personal supplementation of vitamin D along with the study intervention of 400 IU/day, whereas participants in the study reporting positive results were instructed to discontinue the study intervention (833 IU/day) if their provider recommended vitamin D supplement ≥ 200 IU/day. Overall, the evidence was of low quality, with limitations related to uncertain explanation of inconsistent results, small number of trials, and possible lack of statistical power in the study reporting a positive result.

Type 2 Diabetes

Three RCTs evaluated the effect of vitamin D on diabetes outcome measures in healthy adults (Nilas and Christiansen, 1984; de Boer et al., 2008; Grimnes et al., 2011). The study by de Boer et al. was an analysis of data derived from the WHI study; supplementation had no effect on the incidence of diabetes over 7-year follow-up. Grimnes and colleagues enrolled 104 adults (mean age, 52 to 53 years); supplementation for 6 months had no effect on serum levels of glycated hemoglobin. Nilas and Christiansen observed no effect on blood glucose at 1 or 2 years. Vitamin D doses ranged from 400 IU/day plus calcium in the WHI analysis to 2000 IU/day plus calcium or the equivalent of 2857 IU/day without calcium in the other two studies. Baseline serum 25-OHD was reported only by Grimnes and colleagues (mean 39.2 or 42.2 nmol/L by treatment arm).

Summary: One good-quality RCT and 2 fair-quality RCTs suggested that supplementation with vitamin D has no effect on the incidence of diabetes or diabetes markers in adults. The overall quality of the evidence is low due to the small number of studies and intermediate outcome measures in the two smaller studies.

Multiple Sclerosis

No RCTs evaluating the effect of vitamin D supplementation on the incidence of MS were identified.

Mood Disorders

Three fair- to good-quality RCTs (4625 participants) evaluated the effect of vitamin D on mental health in unselected populations (Harris and Dawson-Hughes, 1993; Dumville et al., 2006; Sanders et al., 2011). Participants were all postmenopausal women or elderly adults. Follow-up ranged from 6 months to 5 years, and supplementation regimens ranged from 400 IU/day vitamin D plus calcium to 1370 IU/day vitamin D alone. Baseline serum 25-OHD was not reported for the overall study group in any of these trials. Supplementation had no effect on the mental component score of the SF-12® Health Survey (QualityMetric Inc.) questionnaire (Dumville et al.; Sanders et al.), the Profile of Mood States questionnaire (Harris and Dawson-Hughes), or the General Health Questionnaire (Sanders et al.). A subgroup of 118 participants was also assessed according to the World Health Organization Well-Being Index and the Patient Global Impression Improvement Scale and no treatment effect of vitamin D was apparent (Sanders et al.).

In a fair-quality study (n=441) that enrolled only obese patients (see Appendix Vb), vitamin D3 at the equivalent of 5714 or 2857 IU/day had a beneficial effect on depression scores according to per-protocol analysis but not according to intention-to-treat (ITT) analysis (Jorde et al., 2008). Most participants were not categorized as depressed at baseline.

Summary: Two large good-quality RCTs and one fair-quality RCT (4625 participants) provided consistent evidence suggesting that supplementation with vitamin D across a wide range of doses has no effect on the risk of depression or other mood disorders in older adults. The overall body of evidence is of moderate quality.

All-Cause Mortality

Two RCTs evaluated the effect of vitamin D on all-cause mortality (Trivedi et al., 2003; LaCroix et al., 2009). LaCroix et al. provided an analysis of data derived from the WHI study, which randomized 36,282 postmenopausal women to daily supplementation with 400 IU vitamin D plus calcium or placebo for 7 years (LaCroix et al., 2009). (NOTE: The same WHI results pertaining to all-cause mortality were also reported by Wactawski-Wende et al. [2006].) The other study comprised 2686 elderly participants (mean age, 74 years) who were randomized to placebo or 100,000 IU vitamin D every 4 months (approximately 833 IU/day) for 5 years (Trivedi et al., 2003). Estimates of RR favored vitamin D in both studies but were statistically nonsignificant: RR, 0.88 (95% CI, 0.74 to 1.06) (Trivedi et al.); HR, 0.91 (95% CI, 0.88 to 1.01) (LaCroix et al.). Neither study reported baseline serum 25-OHD.

A Cochrane Review pooled data from 50 RCTs (94,148 participants) to assess the effect of vitamin D supplementation on mortality in adults (Bjelakovic et al., 2011). This review was not considered in detail or included in the evidence tables because the studies were not analyzed according to population or indication and thus the results are not directly applicable to either a healthy or a disease population. There was an overall finding that vitamin D decreased mortality by a small factor (RR, 0.97; 95% CI, 0.94 to 1.00; no heterogeneity).

Summary: Two large good-quality studies representing low and standard vitamin D doses showed supplementation with vitamin D to have a small effect on all-cause mortality. A significant percentage of participants (approximately 28%) in the study by Trivedi et al. (2003) had CVD at baseline, so the study population may not fit into the “generally healthy” population category. The 2 trials differed with respect to whether participants were allowed to combine the study intervention with nonstudy vitamin

D. The overall quality of the evidence is low due to few studies, variation in treatment protocols, and somewhat limited applicability to a healthy population. The results are consistent with findings from a systematic review that evaluated the effect of vitamin D supplementation on mortality in adults without a distinction between patients with and without baseline disease.

Outcomes Related to Pregnancy and Lactation

Four RCTs (422 randomized women), reported in 5 publications, evaluated the effect of maternal vitamin D supplementation on growth-related outcome measures in infants (Brooke et al., 1980; Maxwell et al., 1981; Mallet et al., 1986; Marya et al., 1988; Wagner et al., 2006). Three studies assessed the effect of supplementation during late pregnancy on anthropometric measures at birth (Brooke et al., 1980; Mallet et al., 1986; Marya et al., 1988). In the 2 studies involving a daily supplement of 1000 IU/day, no effect on anthropometric measures was detected (Brooke et al., 1980; Mallet et al., 1986). However, in the study that prescribed one-time administration of 600,000 IU per month during the seventh and/or eighth month of pregnancy, small but statistically significant differences favoring the vitamin D group were observed (Marya et al., 1988). Marya and colleagues also found that the incidence of low birth weight was lower in the vitamin D group (4% versus 19%, significance testing not reported). Supplementation with vitamin D was associated with a significantly smaller fontanel area (4.1±0.4 cm versus 6.1±.7 cm; $P<0.05$) in the only study that reported this measurement (Brooke et al., 1980).

In a fourth poor-quality RCT, 19 lactating mothers who had received prenatal supplements containing 400 IU vitamin D were randomized to receive placebo or an additional 6000 IU vitamin D daily for 6 months (Wagner et al., 2006). Infants of mothers in the control group received 300 IU/day and infants of mothers in the vitamin D group received placebo daily. Maternal vitamin D supplementation had no effect on infant weight, head circumference, or length at 1, 4, and 7 months. Maternal baseline serum 25-OHD levels were high (mean 80 or 85 nmol/L by treatment arm).

Summary: Two small good-quality RCTs suggested that late pregnancy maternal vitamin D supplementation at doses of 1000 IU/day has no effect on newborn size, whereas a single small good-quality RCT suggested that large doses of maternal vitamin D (600,000 per month) in late pregnancy improved birth size and weight. A single poor-quality RCT that randomized both lactating mothers and infants to vitamin D or placebo found no effect on infant growth. The overall quality of the evidence is low for vitamin D during pregnancy due to the quantity and size of the studies and very low for vitamin D during lactation for similar reasons, as well as substantial loss to follow-up.

Young Children

Other than the study of supplementation in lactating mothers by Wagner et al. (2006) (see previous discussion), only 1 RCT evaluating the effect of supplementation in young children was identified. A large RCT conducted among low-birthweight infants in India demonstrated that a high dose of vitamin D (1400 IU/day) over a 6-month period improved most anthropometric measures (Kumar et al., 2011). Health outcomes were not affected during the 6-month period. Loss to follow-up was high and occurred more often with infants from poorer and less well-educated households. Baseline serum 25-OHD levels were not reported.

Older Children and Adolescents

No eligible RCTs evaluating the nonskeletal effects of vitamin D supplementation on the growth-related outcome measures in older children and adolescents were identified.

Summary: Effectiveness of Vitamin D Screening in Healthy Populations (Key Question #2a)

No trials designed to directly measure the clinical effectiveness of vitamin D screening were identified. Trials of vitamin D supplementation were reviewed as an indication of the *potential* utility of vitamin D screening.

Evidence suggests a benefit from supplementation (low-quality evidence)

- *Musculoskeletal health in older adults*, especially when combined with calcium: improved BMD (9 RCTs), reduced risk of falls (1 meta-analysis of 26 RCTs; 46,782 participants); reduced risk of fracture if vitamin D is combined with calcium (1 meta-analysis of 11 RCTs; 52,915 participants). Participants were predominantly postmenopausal women.
- *Reduction of mortality in older adults* (2 RCTs; 38,968 participants, predominantly postmenopausal women). Findings are consistent with a systematic review of studies involving adults (all ages) with and without baseline disease.

Evidence suggests no benefit from supplementation (low- to moderate-quality evidence)

- *Prevention of diabetes in adults* (2 RCTs; 33,951 postmenopausal women and 342 middle-aged adults) (low quality).
- *Prevention of mood disorders in adults* (3 RCTs, 4625 participants) (moderate quality).

Uncertain benefit from supplementation (low-quality evidence primarily because of inconsistency in study results)

- *Bone health in infants, children, and adolescents*: BMC and BMD (cumulative evidence in 3 systematic reviews).
- *Prevention of obesity in adults* (3 RCTs; 36,687 participants).
- *Prevention of cancer in older adults* (may vary by cancer type) (3 RCTs; 40,165 participants, predominantly postmenopausal women).
- *Prevention of cardiovascular disease in older adults* (2 RCTs; 38,968 participants, predominantly postmenopausal women).
- *Promotion of greater birth size and weight* through maternal supplementation in *late pregnancy* (3 RCTs; 422 participants).

Insufficient evidence regarding a benefit from supplementation (no evidence or single small trials)

- *Prevention of multiple sclerosis (MS).*
- Improvement of *nonskeletal health outcomes* in *younger adults, lactating women, infants, children, and adolescents*.

Quality and relevance of the evidence pertaining to supplementation

Evidence for each general outcome is of low quality with respect to the benefit of supplementation (one exception: moderate-quality evidence regarding prevention of mood disorders). Common weaknesses included estimates of relative risk that favored vitamin D but were statistically nonsignificant; variable vitamin D doses across studies, with studies using low doses more likely to report negative or nonsignificant results; and varied protocols with respect to the use of nonstudy vitamin D. There was a dearth of evidence pertaining to younger populations. Where the evidence suggested a benefit, the effects were small.

Implications for vitamin D screening

Given the evidence suggesting positive effects of supplementation on *musculoskeletal* health and general mortality in older adults, screening for low vitamin D status might be effective for these particular outcomes, but that would depend on whether effects vary according to baseline serum levels. Evidence, to date regarding the effectiveness of increased vitamin D intake through supplementation does not, in general, support vitamin D screening to improve *nonskeletal* health outcomes other than mortality. However, an analysis of differential effectiveness by patient risk factors and baseline serum levels could modify this conclusion. See Findings for Key Question #4a.

Key Question #2b: Is there evidence that testing for serum vitamin D levels as a routine screening test in patients with *chronic disease* improves health outcomes (clinical utility)?

Findings

As noted in the METHODS section of this report, the literature does not provide direct evidence of the effectiveness of vitamin D screening or testing. Three systematic reviews and 16 RCTs (18 publications) evaluating the effect of vitamin D supplementation on disease-related outcomes in the populations of interest were identified; details are provided in Appendices Va and Vb. The study participants were not selected on the basis of vitamin D test results.

Obesity

Eight RCTs involving 5 study populations and 32,111 randomized participants were selected (Caan et al., 2007; Major et al., 2007; Jorde et al., 2008; Sneve et al., 2008; Major et al., 2009; Zittermann et al., 2009; Jorde et al., 2010; Rosenblum et al., 2012). Participants were generally in early middle age and all had a BMI > 25 kilograms per meter squared (kg/m^2); more women than men were included. Vitamin D dosage varied greatly: 300 IU/day, 400 IU/day (including the largest study), 20,000 IU or 40,000 IU weekly (equivalent to 2857 or 5714 IU/day), and 3332 IU/day. Most participants received calcium supplementation as well. The studies showed no effect on diastolic blood pressure (2 study groups), conflicting results regarding effect on systolic blood pressure (no effect in 1 study and harmful effect in 1 study), glycemia measures (3 study groups), weight (3 study groups), or other measures of obesity (2 study groups). One study (Jorde et al., 2010) reported inconsistent evidence of an effect on the risk of diabetes in the subgroup of individuals with impaired glucose tolerance at baseline. No studies analyzed the effect on blood pressure according to baseline values. One study (Jorde et al., 2008) found that vitamin D3 had a beneficial effect on depression scores according to per-protocol analysis but no significant effect according to ITT analysis.

Summary: Data from 5 small to large RCTs (total, n=32,111) provided consistent evidence suggesting that vitamin D at doses of 300 to 5714 IU/day has *no effect* on weight-related outcomes or

cardiometabolic outcomes in obese adults. Study quality was generally good in the analyses involving > 400 participants but was fair in smaller studies, with the chief limitation being dropout rates exceeding 20% and no ITT analysis. Overall evidence pertaining to weight and cardiometabolic outcomes is of moderate quality and conclusions could change if additional large trials using doses in the higher range were conducted, especially with the analysis of baseline measures of blood pressure and glycemia. Evidence pertaining to more ultimate health outcomes, such as mortality or cardiovascular events, in obese individuals is lacking.

Poor Musculoskeletal Health

Measurement of serum vitamin D in a population defined by evidence of poor bone health, such as low BMD, a history of nontraumatic fracture, or a history of falls, would be considered testing rather than screening. The AHRQ reports (Cranney et al., 2007; Chung et al., 2009; Chung et al., 2011) selected trials in which patient selection was not based on the absence or presence of poor bone health. However, a recent Hayes report evaluated vitamin D supplementation for patients with osteoporosis (Hayes, 2012). The report included 17 controlled RCTs (2547 participants). The study participants were generally vitamin D deficient and were selected on the basis of a diagnosis of osteoporosis or indirect evidence of poor musculoskeletal health (e.g., history of vertebral fracture). Most of the included studies evaluated active forms of vitamin D. In two RCTs evaluating vitamin D3 (inactive vitamin D) plus calcium in patients with a history of fracture consistent with osteoporosis, the effect on BMD at different sites varied widely; where positive effects were observed, they were very small. Active vitamin D, on the other hand, was found to be effective in maintaining or improving BMD compared with control groups (3 RCTs) and more effective than inactive vitamin D for maintaining or improving BMD and/or reducing fractures and falls (2 RCTs; vitamin D groups were prescribed doses of 800 and 1400 IU/day of vitamin D3). Active vitamin D was less effective than bisphosphonates in four RCTs and less effective than hormone replacement therapy in one RCT. However, five RCTs showed that active vitamin D as an add-on to either bisphosphonate or hormone replacement therapy (HRT) was more effective than bisphosphonates or HRT alone.
A meta-analysis conducted for the 2011 AHRQ report suggested that, although inactive vitamin D plus calcium was effective in reducing the incidence of fracture in older adults (11 RCTs), it may not be effective in community-dwelling adults with a history of fracture (2 RCTs different from the 2 RCTs of inactive vitamin D3 in the 2012 Hayes report) (Chung et al., 2011). The 2 RCTs involving individuals with a history of fracture evaluated vitamin D3 at 800 IU/day.

A subgroup analysis of the WHI study group revealed that although supplementation with vitamin D (400 IU/day) plus calcium was not generally effective, it might be effective in postmenopausal women with a history of ≥ 3 fractures (HR, 2.51; CI, 0.97 to 6.48; n=22) (Jackson et al., 2006). However, this evidence is too sparse to allow a conclusion about the effectiveness of vitamin D supplementation in individuals with an extreme history of fracture.

Summary: Evidence from two systematic reviews suggested that *inactive* vitamin D at doses of 800 to 1400 IU/day is not effective for improving bone health in patients who have a history of fracture (4 RCTs). The available body of evidence does not address the question of megadoses (e.g., 50,000 IU/week) of inactive vitamin D. Trials using *active* forms of vitamin D (calcitriol or synthetic analogs) (15 RCTs) have reported more positive results. Active vitamin D has been shown to be effective in individuals with osteoporosis or a history of fracture. Active forms of vitamin D also improve the effectiveness of other forms of pharmaceutical treatment for poor bone health (bisphosphonates and HRT). Given the volume of evidence and trial quality as described by the review authors, the overall

quality of evidence is moderate. (NOTE: If BMD is considered an intermediate outcome and the incidence of fractures and falls the true health outcome, then evidence should be considered to be of low quality.)

Cancer

A single systematic review evaluating vitamin D in cancer patients was identified (Buttigliero et al., 2011). The review identified 3 RCTs, all of which involved patients with advanced prostate cancer. The results pertaining to overall survival were conflicting and a meta-analysis yielded null RRs with wide CIs. The authors' assessment of study quality suggests that the studies were of fair quality. Two studies were subject to bias because of early stopping based on interim analysis.

The literature search conducted for the current evidence report found no RCTs of vitamin D in cancer patients after the search time frame reported by Buttigliero et al. (2011).

Summary: Low-quality evidence from 3 fair-quality RCTs (total, n=1273) neither confirms nor rules out a beneficial effect of supplementation with active vitamin D on survival in patients with advanced prostate cancer. The results were inconsistent and pooled estimates were imprecise. No evidence pertaining to other types of cancer were identified.

Cardiovascular Disease

A systematic review evaluating the effect of vitamin D supplementation on blood pressure identified 7 RCTs (< 545 participants) involving participants with hypertension (defined as systolic blood pressure > 140 millimeters of mercury [mm Hg], diastolic blood pressure > 90 mm Hg, or mean arterial pressure < 105 mm Hg) (Witham et al., 2009). Inactive vitamin D doses fell within the range of 800 to 2000 IU/day (D2 and D3). A meta-analysis of the difference in blood pressure change suggested a small beneficial effect: –3.3 mm Hg (CI, –8.2 to 1.7) for systolic blood pressure and –2.3 mm Hg (CI, –4.6 to 0.0) for diastolic blood pressure. The authors cited evidence suggesting that a reduction in systolic blood pressure of 3 mm Hg would correspond to 10% reduction in cardiovascular deaths on a population level. Subgroup analysis suggested a greater effect on systolic blood pressure in trials using inactive vitamin D (D2 or D3) than in trials using active vitamin D (calcitriol or synthetic analogs), but the difference in the effect between the two trial subgroups was not significant.

Two RCTs evaluating vitamin D in patients with congestive heart failure were selected. A poor-quality RCT (n=93 evaluable patients) with a substantial withdrawal of sicker patients detected no difference in biochemical and hemodynamic measures at 9 months and no difference in cumulative survival at 15 months, comparing vitamin D3 (2000 IU/day) plus calcium with calcium plus placebo (Schleithoff et al., 2006). Another RCT (n=105) of good quality randomized patients with chronic heart failure to 2 administrations of 100,000 IU of vitamin D2 at baseline and 10 weeks, or placebo, in order to assess the effect on function and quality of life (QOL) (Witham et al., 2010). Baseline scores were very similar between groups. At 20 weeks, there was no difference in scores according to the Functional Limitations Profile or 6-minute walk time but a significant and meaningful difference favoring vitamin D2 on the Minnesota Living With Heart Failure Questionnaire.

Where reported, mean baseline serum 25-OHD values in the studies included by Witham et al. (2009) and in the other two trials ranged from 25 to 48 nmol/L.

Summary: A meta-analysis of 7 small RCTs without serious limitations suggested a small but clinically meaningful reduction in systolic blood pressure associated with vitamin D supplementation and an uncertain effect on diastolic blood pressure in patients with hypertension. In patients with congestive heart failure, a poor-quality RCT detected no effect on physiological measures or survival, while a good-quality RCT detected a small benefit in QOL but no effect on measures of function. The 2 RCTs evaluating patients with congestive heart failure were heterogeneous with respect to type of vitamin D therapy. Considering blood pressure to be an important outcome measure with known links to more ultimate cardiovascular events, the overall body of evidence pertaining to vitamin D and cardiovascular disease is of moderate quality.

Type 2 Diabetes

Two systematic reviews were selected for identification of RCTs involving individuals with abnormal blood glucose (frank diabetes, impaired glucose control, or insulin resistance) and published prior to 2009 (Pittas et al., 2010; George et al., 2012). Eight RCTs (707 participants) conducted in populations with abnormal blood glucose were included. Both reviews had well-defined search strategies and selection criteria and provided key individual study results as well as assessments of study quality. Both conducted meta-analyses, but only the review by George et al. provided meta-analyses specific to populations with abnormal blood glucose. An additional 4 RCTs (297 randomized participants) were selected involving patients with frank type 2 diabetes (Eftekhari et al., 2011; Nikooyeh et al., 2011), abnormal blood glucose and high risk of type 2 diabetes (Mitri et al., 2011b), or gestational diabetes (Mozaffari-Khosravi et al., 2012). Active vitamin D or very high doses of inactive vitamin D were used in these trials. Most trials did not combine calcium with vitamin D. Baseline serum 25-OHD ranged from 20 to 95 nmol/L.

The results from the 12 RCTs varied, but no studies showed harmful effects. Among 11 trials that reported measures of glycemia (fasting plasma glucose or HbA1C) or insulin resistance, the estimates of differences in change between vitamin D and control groups consistently favored vitamin D but ranged from negligible in magnitude and statistically nonsignificant to uncertain because of very wide CIs to statistically significant but small in magnitude. One of the trials included in the two reviews detected an effect in the subgroup with impaired glucose tolerance (included in the following pooled estimates) but not in the subgroup with normal fasting glucose at baseline (not included in the results presented here). A meta-analysis of the RCTs included in systematic reviews resulted in significant standardized effect size estimates for two of three measures, all without statistical heterogeneity (George et al., 2012):

- Change in fasting plasma glucose: –0.32 (95% CI, –0.57 to –0.07) (4 RCTs)
- Change in HbA1C: –0.25 (CI, –0.48 to –0.03) (6 RCTs)
- Change in insulin resistance: 0.03 (CI, –0.18 to 0.23) (4 RCTs)

(Estimates represent standardized mean differences, vitamin D minus placebo.)

In the 4 RCTs published after the review by George et al. (2012), the results regarding glycemic control (Mitri et al., 2011b; Nikooyeh et al., 2011; Eftekhari et al., 2012; Mozaffari-Khosravi et al., 2012) and insulin resistance (Nikooyeh et al.; Eftekhari et al.) were mixed: no significant effect on glycemia or insulin resistance in 1 trial (Eftekhari et al.), no effect on glycemia but a meaningful effect on insulin resistance in 1 trial (Mozaffari-Khosravi et al.), and small positive effects on both glycemia and insulin resistance in 2 trials (Mitri et al.; Nikooyeh et al.).

Two trials included in the reviews by Pittas et al. (2010) and George et al. (2012) plus a more recently published trial (Nikooyeh at al., 2011) evaluated the effect of vitamin D supplementation on blood pressure in patients with frank diabetes. Between-group differences were negligible and nonsignificant in all 3 trials.

One study demonstrated small but significant effects on several measures related to obesity in patients with frank diabetes (Nikooyeh et al., 2001). A single trial reported by George et al. (2012) found no effect on albuminuria.

Summary: Eleven small RCTs, 8 of which were reported in two systematic reviews and included in a meta-analysis, generally suggested that vitamin D supplementation at high doses or in active form may have very small beneficial effects on glycemic control in individuals with abnormal blood glucose. However, evidence from 6 RCTs evaluating an effect on insulin resistance was inconsistent. Three trials were consistent in showing no effect on blood pressure. Trial quality was generally fair. The chief limitation was a lack of statistical correction for multiple testing: authors analyzed a large number of outcome measures, which increases the possibility that some effects were significant by random chance only. The body of evidence is of moderate quality for effect on glycemia and blood pressure but of low quality because of inconsistency for an effect on insulin resistance. Evidence pertaining to other outcomes, such as weight control or renal function, is insufficient. Considering glucose control and blood pressure to be important intermediate outcomes with known links to more ultimate outcomes, the overall body of evidence is of moderate quality.

Multiple Sclerosis

Five reports of 4 RCTs involving 150 randomized men and women with a diagnosis of MS were selected (Mahon et al., 2003; Burton et al., 2010; Kimball et al., 2011; Mosayebi et al., 2011; Soilu-Hänninen et al., 2012). Two studies demonstrated that vitamin D plus calcium was associated with changes in anti-inflammatory markers (Mahon et al., 2003) or reduction in response to 7 of 17 antigens (Kimball et al., 2011), and 1 study (Soilu-Hänninen et al., 2012) found an effect favoring vitamin D alone on two of several MRI findings. Three studies reported conflicting results for clinical outcomes (Burton et al., 2010; Mosayebi et al., 2011; Soilu-Hänninen et al., 2012). In the study by Burton et al., patients taking vitamin D *plus calcium* were less likely (26%) to have relapsed at 1 year than were patients who were not prescribed supplementation (45%), but the study was underpowered to detect a significant difference. The supplemented group was also less likely (8%) to have a higher Expanded Disability Status Scale (EDSS) score at 1 year than was the control group (37.5%), and this difference was significant (P=0.019). Burton and colleagues allowed all of the patients to continue personal use of supplements. Mosayebi and colleagues, who compared vitamin D *alone* with *placebo* observed no significant within- or between-group changes in EDSS (or number of lesions) at 7 months. Soilu-Hänninen and colleagues observed no statistically significant effect of vitamin D *alone* on EDSS score, walking tests, or relapse rates, although the results for the functional measures favored the vitamin D group. Differences regarding clinical outcomes may be related to the combination of calcium with vitamin D in the more positive study and/or lack of power in the studies with negative results.

It should be noted that individuals with MS are often treated with corticosteroids, which are known to contribute to bone loss. See *Poor Musculoskeletal Health* for a discussion of Key Question #2b as it relates to individuals with osteoporosis.

Summary: Data from 2 fair-quality RCTs suggested that vitamin D plus calcium has positive effects on physiological, clinical, and functional disease-related outcomes in MS patients. A good-quality RCT and a fair-quality RCT detected no effect on health outcomes from vitamin D alone. The overall body of evidence is of low quality due to the small quantity of data, which is insufficient to allow confident conclusions about the reasons for conflicting results.

Depression and Other Mood Disorders

Two RCTs conducted in individuals with mood disorders (Gloth et al., 1999; Khajehei et al., 2009) were identified but did not meet the inclusion criterion because of follow-up interval < 3 months, sample size < 20, and/or lack of calcium only or placebo control group. Abstracts for these publications were reviewed. One study of 15 individuals with seasonal affective disorder (SAD) showed that vitamin D plus calcium improved symptoms after 1 month, whereas phototherapy did not (Gloth et al., 1999). In another study of 180 college-age women with premenstrual syndrome (PMS), calcium plus vitamin D was comparable with hormone therapy, but compared with placebo, neither treatment had more than a very small effect on symptoms after 2 months (Khajehei et al., 2009).

All-Cause Mortality

No data on all-cause mortality were reported in the selected studies and systematic reviews.

Summary: Effectiveness of Vitamin D Testing and Screening in Populations with Chronic Disease (Key Question #2b)

No trials designed to directly measure the clinical effectiveness of vitamin D screening were identified. Trials of vitamin D supplementation were reviewed as an indication of the *potential* utility of vitamin D testing and screening.

Evidence suggests a benefit from supplementation (moderate-quality evidence):

- Improvement of bone health in *older patients with osteoporosis or history of fracture using active forms of vitamin D* (15 RCTs).
- Improvement of disease-related outcomes *in patients with CVD* (8 RCTs).
- Improvement of disease-related outcomes *in patients with abnormal blood glucose* (type 2 diabetes, impaired glucose tolerance, or insulin resistance (12 RCTs).

Evidence suggests no benefit from supplementation (moderate-quality evidence):

- Bone health in *patients with osteoporosis or history of fracture using inactive vitamin D* (4 RCTs).
- Weight-related and cardiometabolic outcomes in *obese adults* (5 RCTs; moderate-quality evidence).

Uncertain benefit from supplementation (low-quality evidence because of inconsistency in direction of study results or inconclusive pooled estimates):

- Survival in patients with *advanced prostate cancer* (3 RCTs).
- Disease-related outcomes in patients with *MS* (4 RCTs).

<u>Insufficient evidence</u> regarding a benefit from supplementation (no evidence or single small RCTs):

- Patients with *cancer other than prostate cancer.*
- Individuals with *depression or another mood disorder*.
- *All-cause mortality* in any population.

Quality and relevance of the evidence regarding supplementation

Evidence ranged from low to moderate quality, depending on the disease population. It should be noted that even in the disease populations where the evidence showed a benefit, *the effects were generally small and may not be clinically relevant* (an exception was the effects of active vitamin D supplementation on bone health in older adults with osteoporosis or a history of fracture).

Implications for vitamin D testing and screening

Given the evidence of the effectiveness of active forms of vitamin D, vitamin D testing in patients who have evidence of osteoporosis has the potential to improve bone-related outcomes. Given the evidence showing supplementation to modestly improve disease-related outcomes in individuals with cardiovascular disease or abnormal blood glucose, vitamin D screening to assess the risk of adverse disease outcomes might be effective in these populations. However, a conclusion that testing or screening is effective in these clinical situations depends on whether the effectiveness of supplementation varies according to baseline serum levels. Evidence, to date, regarding the effectiveness of increased vitamin D intake through supplementation does not, in general, support screening in other disease populations. However, an analysis of differential effectiveness by patient risk factors and baseline serum levels could modify this conclusion .See Findings for Key Question #4b.

Key Question #3: Are there harms associated with vitamin D testing or with subsequent supplementation?

Findings

Vitamin D testing relies on a blood draw, which is a safe procedure. The consequences of inaccurate or inappropriately interpreted results are relatively small. Since vitamin D has at best relatively modest effects, safety issues associated with false-negative test results would be minimal. Since vitamin D supplementation is a relatively safe therapy (see following discussion), the consequences of false-positive test results would not be serious.

Vitamin D toxicity resulting in kidney and other tissue damage is possible, but no adverse events have been reported at doses < 10,000 IU/day (Aloia, 2011). The IOM has set 4000 IU/day as the Tolerable Upper Intake Level (UL) (IOM, 2011). The doses used in the trials covered in this evidence report were well within the UL.

The individual trials reviewed for this report did not discuss adverse events, indicated that none were reported, or found no important difference between supplementation and placebo groups. The best trial data regarding adverse effects comes from the WHI trial, which randomized 36,282 women to 400

IU/day of vitamin D plus calcium or placebo and followed them for 7 years. Trial data did show an increased risk of kidney stones (HR, 1.17; 95% CI, 1.02 to 1.4; *P*=0.02), but self-reported symptoms such as moderate to severe abdominal symptoms were similar between groups (Wactawski-Wende et al., 2006).

The authors of the 2011 AHRQ report (Chung et al., 2011) noted that of the 19 RCTs in the 2011 review and 63 RCTs included in the 2009 predecessor report (Chung et al., 2009), few reported information about adverse events. Other than renal stones, the selected RCTs reported a few cases of constipation, diarrhea, upset stomach, musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi, but Chung et al. (2011) noted that these events may or may not be associated with vitamin D or calcium supplements. A systematic review and meta-analysis of interventions to prevent falls in community-dwelling adults reported that in the 3 RCTs (926 participants) that assessed harms, some patients experienced transient and asymptomatic hypercalciuria or hypercalcemia, but no between-group differences in kidney stones, cancer, ischemic heart disease, or stroke (Michael et al., 2010).

A Cochrane Review of vitamin D supplementation and mortality reported estimates showing an increased risk of hypercalcemia: for inactive forms of vitamin D (12 trials; 11,091 participants), HR, 1.26 (95% CI, 0.78 to 2.05) and for active forms of vitamin D (3 trials; 410 participants), HR, 3.18 (95% CI, 1.17 to 8.68) (Bjelakovic et al., 2011).

Summary: Safety of Vitamin D Screening/Testing and Supplementation (Key Question #3)

Vitamin D testing is a safe procedure, and vitamin D therapy is a reasonably safe treatment. Supplementation with inactive vitamin D is associated with a moderate increase in the risk of both hypercalcemia and kidney stones, which are related conditions. Treatment with active (pharmaceutical) vitamin D is associated with an approximately threefold increase in the risk of hypercalcemia. Vitamin D therapy may be associated with musculoskeletal and gastrointestinal symptoms, but a causal relationship has not been proven, and no serious adverse events have been reported in trials of vitamin D supplementation.

Quality of the evidence

Considering the quantity of data, consistency of results, and the quality of individual studies (as directly assessed and as reported by systematic reviews), the body of evidence concerning the safety of vitamin D is of moderate quality, and the quality of the evidence concerning the safety of active is of low quality due to a smaller quantity of data.

Key Question #4a: What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in *healthy* populations?

As previously noted, no trials were found that assessed the effect of vitamin D screening or testing on health outcomes, patient behavior, or clinical decisions. Thus, there is no direct evidence regarding the differential effectiveness and safety of vitamin D screening or testing. The RCTs selected for evidence of the effectiveness of vitamin D supplementation in healthy populations served as evidence of whether the *potential* effectiveness and safety of vitamin D screening might differ according to patient

characteristics or testing parameters. The bulk of evidence is derived from focused analyses of the WHI study, which involved 36,282 postmenopausal women (all older than 50 years of age) who were randomized to vitamin D (400 IU/day) plus calcium and followed for 7 years. As noted in the discussion of findings for Key Question #2a, the prevalence of vitamin D insufficiency was much greater in the WHI trial population (estimated 72% with 25-OHD levels < 52.4 nmol/L) than in the general population of American women aged 50 years or older (28% with levels < 50 nmol/L).

Findings

Patient Characteristics

Sex: In a meta-analysis of 9 RCTs conducted in older community-dwelling adults, with vitamin D doses that were generally ≥ 800 IU/day, there was no differential effect on the risk of falls by sex (Michael et al., 2010). In a meta-analysis of 6 RCTs conducted in children and adolescents with vitamin D doses of 132 to 2100 IU/day, the effect on BMD did not differ between boys and girls (Winzenberg et al., 2011). None of the other systematic reviews of vitamin D supplementation and bone health and none of the primary studies evaluating nonskeletal outcomes reported differential effects by sex.

Age or Life Stage: In a meta-analysis of 9 RCTs conducted in older community-dwelling adults, with vitamin D doses that were generally ≥ 800 IU/day, there was no differential effect on the risk of falls by age (Michael et al., 2010). In various analyses of the WHI (vitamin D at 400 IU/day), no differential effect by age was detected for risk of fracture (Jackson et al., 2006), weight control (Caan et al., 2007); risk of invasive CRC (Wactawski-Wende et al., 2006); risk of melanoma or nonmelanoma skin cancer (Tang et al., 2011); risk of invasive cancer overall (Brunner et al., 2011); cancer death (LaCroix et al., 2008); death from CVD, CAD, or cerebrovascular disease (LaCroix et al., 2008); risk of hypertension (Margolis et al., 2008); risk of diabetes (De Boer et al., 2008); death from other causes or unknown causes (LaCroix et al., 2008); or overall mortality (LaCroix et al., 2008). These analyses generally apply to elderly adults; given the populations in which supplementation has most frequently been studied, age comparisons across a wide range of adult ages is not possible.

In a meta-analysis of 6 RCTs conducted in children and adolescents with vitamin D doses of 132 to 2100 IU/day, the effect did not differ between prepubertal children and adolescents (Winzenberg et al., 2011). None of the other systematic reviews of vitamin D supplementation and bone health reported differential effects by sex.

Race or Ethnicity: Analyses of the WHI study detected no differential effect by race/ethnicity on risk of fracture (Jackson et al.,. 2006); weight control (Caan et al., 2007); risk of invasive CRC (Wactawski-Wende et al., 2006); risk of invasive cancer overall (Brunner et al., 2011); risk of hypertension (Margolis et al., 2008); a composite measure of MI or CAD death (Hsia et al., 2007); risk of diabetes (De Boer et al., 2008); or total mortality (LaCroix et al., 2008). Authors of the systematic review of vitamin D to improve BMD in children and adolescents (6 RCTs) reported that there were insufficient data to allow assessment of effect according to race/ethnicity (Winzenberg et al., 2010). None of the other systematic reviews of vitamin D supplementation and bone health and none of the primary studies evaluating nonskeletal outcomes reported differential effects by race or ethnicity.

Geographic Location: Analyses of the WHI study detected no differential effect by regional solar exposure on risk of fracture (Jackson et al., 2006); risk of invasive CRC (Wactawski-Wende et al., 2006); by solar radiation on risk of melanoma or nonmelanoma skin cancer (Tang et al., 2011); by latitude or

sun exposure on risk of invasive cancer overall (Brunner et al., 2011); by sun exposure on risk of diabetes (De Boer et al., 2008); or by latitude on total mortality (LaCroix et al., 2008). Authors of the systematic review of vitamin D to improve BMD in children and adolescents (9 RCTs) reported that there were insufficient data to allow assessment of effect according to sun exposure (Winzenberg et al., 2011). None of the other systematic reviews of vitamin D supplementation and bone health reported differential effects by sun exposure.

Dietary Intake: Several analyses of the WHI study evaluated differential effect by total intake of vitamin D and/or calcium, use of vitamin D and/or calcium supplements, use of multivitamins, energy from saturated fat, and/or diet modification to include more fruits and vegetables. No differential effects were discovered for risk of fracture (Jackson et al., 2006); weight control (Caan et al., 2007); risk of invasive CRC (Wactawski-Wende et al., 2006); risk of melanoma or nonmelanoma skin cancer (Tang et al., 2011); risk of hypertension (Margolis et al., 2008); risk of CAD, stroke, or a composite measure of MI or CAD death (Hsia et al., 2007); risk of diabetes (de Boer et al., 2008). In the analysis by Chlebowski et al. (2008), there was a statistically significant trend (*P*=0.003) of a harmful effect on risk of breast cancer at the lowest quartile of vitamin D intake (HR, 1.34; 95% CI, 1.01 to 1.78), diminishing to a protective effect (HR, 0.79; 95% CI, 0.65 to 0.97) at the highest quartile. In the analysis by Brunner et al. (2011), no differential effect by total dietary caloric intake or total calcium on risk of invasive cancer was detected, but vitamin D plus calcium supplementation had a harmful effect (HR, 1.22; 95% CI, 1.02 to 1.45) when total vitamin D intake at baseline was ≥ 600 IU/day, whereas nonsignificant protective or neutral effects were observed in individuals with lower levels of baseline vitamin D intake (*P*<0.04 for treatment-intake interaction); however, multivariate analysis of a nested case-control sample suggested no interaction.

In a systematic review published after the search cutoff date for the current report, subgroup analysis was conducted to test the differential effect of vitamin D supplementation in older adults. Overlapping CIs for RR of both hip and nonvertebral fracture suggested that the effect of vitamin D supplementation, with or without calcium, did not vary according to either the prescribed dose of vitamin D (≤ 400 IU/day versus > 400 IU/day) or the actual total vitamin D intake (4 subgroups) (Bischoff-Ferrari et al., 2012).

Lifestyle Factors: Most analyses of the WHI trial detected no differential effect when subgroups were defined by physical activity, smoking status, and/or alcohol consumption. The outcomes addressed in these analyses were incidence of fracture (Jackson et al., 2006); weight control (Caan et al., 2007); invasive CRC (Wactawski-Wende et al., 2006); risk of invasive cancer overall (Brunner et al., 2011); incident diabetes (de Boer et al., 2008); and total mortality (LaCroix et al., 2008). An exception was a greater treatment effect in past smokers in the analysis by Brunner et al., although no effect according to current smoking status was observed.

Obesity: Analyses of the WHI trial detected no differential effect by baseline BMI category on risk of fracture (Jackson et al., 2006); waist circumference on weight control (Caan et al., 2007); risk of invasive CRC (Wactawski-Wende et al., 2006); risk of invasive cancer overall (Brunner et al., 2011); risk of melanoma or nonmelanoma skin cancer (Tang et al., 2011), risk of hypertension (Margolis et al., 2008); or risk of diabetes (de Boer et al., 2008). On the other hand, Hsia et al. (2007) demonstrated a possible protective effect against a composite measure of MI or CAD death only in obese individuals (BMI ≥ 30 kg/m^2) (HR, 0.91; 95% CI, 0.7 to 1.2), whereas HRs calculated for normal and overweight individuals suggested a harmful effect (*P*=0.04 for treatment-BMI interaction); there was no differential effect by waist circumference.

Baseline 25-OHD Serum Level: Authors of the first AHRQ report on vitamin D and bone health (Cranney et al., 2007) found that only a few trials, the WHI trial being one of them, conducted an analysis of the relationship between baseline serum 25-OHD and BMD, fractures, or falls, and that no relationship was detected. Mean or median baseline serum levels ranged from 25 to 97 nmol/L across trials, but the range within studies that analyzed outcomes by baseline serum level was not reported. In the recently published systematic review by Bischoff-Ferrari et al. (2012), the effectiveness of vitamin D supplementation in reducing fractures increased as baseline serum 25-OHD increased above 30 nmol/L (P<0.001 for trend) after adjustment for confounders. The benefit of supplementation was statistically significant in subgroups with baseline levels > 43 and ≥ 61 nmol/L, with < 30 nmol/L as the reference value. Mean baseline levels ranged from 47 to 54 nmol/L, depending on treatment assignment. There was no analysis of vertebral fractures because they were not documented systematically in any of the eligible trials. The authors did not provide information regarding individual study quality, but the included trials overlapped with those included in the AHRQ reports (Chung et al., 2009; Chung et al., 2011); Chung and colleagues judged the overlapping trials to be of generally fair quality.

The systematic review of vitamin D and prevention of falls (9 RCTs; vitamin D generally ≥ 800 IU/day; older community-dwelling adults) did not find that the effect differed between low-risk and high-risk individuals, with high risk defined as low vitamin D status plus a history of falls, in metaregression analysis (Michael et al., 2010). Mean baseline serum levels were not reported. However, in the more inclusive systematic review (26 RCTs; vitamin D generally 400 to 1000 IU/day; mean age 76 years; any setting), there was a difference in the effect on falls in the studies where participants were vitamin D deficient (OR, 0.53; 95% CI, 0.39 to 0.72), compared with studies where participants were not vitamin D deficient (OR, 0.90; 95% CI, 0.81 to 0.99) (Murad et al., 2011). Murad and colleagues did not supply mean baseline serum. Inclusion of nursing home residents and individuals being treated with analogs and thus potentially a different distribution of vitamin D deficiency may account for the findings of a differential treatment effect in the review by Murad et al. Furthermore, in the absence of author identification of participants with deficiency, Murad and colleagues counted populations with ≥ 2 risk factors for vitamin D deficiency as deficient. Metaregression analysis (12 RCTs) in the 2011 focused AHRQ report showed that fracture risk did not change per 100-IU increase in baseline serum 25-OHD concentration, with vitamin D supplementation doses generally ≥ 800 IU/day and baseline serum levels ranging from 15 to 59 nmol/L, where reported (Chung et al., 2011). The systematic review of vitamin D and BMD in children and adolescents reported generally greater changes when baseline 25-OHD was ≥ 35 nmol/L but a nonsignificant difference when change in the subgroup with baseline levels ≥ 35 nmol/L was compared with the change in the subgroup with levels < 35 nmol/L (Winzenberg et al., 2011).

The differential effect of supplementation according to baseline serum 25-OHD has also been evaluated with respect to several nonskeletal outcomes in studies analyzing the WHI trial. Differential effect on risk of invasive colorectal cancer (CRC) (Wactawski-Wende et al., 2006), hypertension (Margolis et al., 2008), and diabetes (de Boer et al., 2008), as well as all-cause mortality (La Croix et al., 2008), was evaluated. The association of supplementation with outcomes varied from protective to harmful across tertiles and quartiles of baseline serum values. However, in the two studies where the interaction between treatment assignment and baseline serum value was statistically significant, trends were in the opposite direction: a possible benefit only at baseline leves < 31.00 nmol/L for risk of CRC (Wactawski et al.) and a possible benefit only at baseline levels ≥ 64.7 nmol/L for risk of hypertension (Margolis et al.) Even though variation was suggested, the effect of supplementation was not statistically significant within any stratum of baseline values in any of the studies. The analysis of all-cause mortality (LaCroix et al.) showed a trend in the same direction as that for risk of CRC. Results for diabetes (de Boer et al.) did

not follow any pattern. l A small trial evaluating the effect of vitamin D-fortified milk on weight change in men (mean age, 61 years) detected no effect overall or in the subgroup who had baseline 25-OHD < 75 nmol/L (Daly and Nowson, 2009). Mean baseline serum levels were 78 or 67 nmol/L, depending on treatment assignment.

A trial of single-dose vitamin D (500,000 IU) per year found that the effect of supplementation on general measures of mental health did not vary by baseline serum 25-OHD in a subgroup of individuals who underwent serum tests (Sanders et al., 2011). Baseline values in the subgroup were 45 to 53 nmol/L by treatment arm.

Many studies of supplementation did not report baseline serum levels, and the results from the studies that did report baseline serum levels did not reveal a clear pattern. There were isolated instances where baseline serum levels were high and no effect of supplementation was detected, but the lack of baseline serum data in the other studies of the same population and outcome prohibit conclusions.

Baseline Disease-Specific Risk: The systematic review of vitamin D and prevention of falls (9 RCTs; vitamin D generally ≥ 800 IU/day; older community-dwelling adults) did not find that the effect differed between individuals with and without a history of falls in metaregression analysis (Michaels et al., 2010). However, an analysis of data from the WHI trial suggested that although supplementation with vitamin D plus calcium was not generally effective, it might be effective in postmenopausal women with a history of ≥ 3 fractures (HR, 2.51; CI, 0.97 to 6.48; n=22) (Jackson et al., 2006).

Some analyses of the WHI study detected no differential effect according baseline risk. There was no differential effect according to history of polyp removal or having a first-degree relative with colorectal cancer on risk of invasive colorectal cancer (Wactawski-Wende et al., 2006); according to cancer history on melanoma or nonmelanoma skin cancer (Tang et al., 2011); according to CAD risk factors or presence of CAD at baseline on a composite measure of MI or CAD death (Hsia et al., 2007); according to family history of diabetes, fasting plasma glucose (FPG) at baseline, or metabolic syndrome on risk of diabetes (de Boer et al., 2008); or by baseline blood pressure, number of chronic conditions, or self-reported health status on total mortality (LaCroix et al., 2008). Two analyses differed from this pattern. A protective effect (HR, 0.84; 95% CI, 0.72 to 0.97) against invasive cancer overall was observed in individuals who had a first-degree relative with invasive cancer but not in individuals who did not (*P*=0.018 for treatment-family history interaction) (Brunner et al., 2011). The effect on stroke increased as the number of baseline CAD risk factors increased (*P*=0.02 for treatment-risk factor interaction) (Hsia et al., 2007).

Testing Parameters

No studies directly evaluated the effectiveness of testing. Therefore, differential effectiveness and safety by type of assay, frequency of monitoring, and time of year that tests are conducted could not be directly evaluated.

- The trials that assessed the relationship between baseline serum 25-OHD and a treatment effect from vitamin D supplementation used assays that are often considered reference standards (competitive protein binding [CPB] assays, chromatographic assays, radioimmunoassay [RIA]).
- Most supplementation trials spanned all seasons of the year, but none analyzed effects by season.

Treatment Parameters

Although this consideration is not included in the Key Questions, indirect evidence from supplementation trials was considered for insight into the treatment factors that might be associated with improvement in outcomes. Such evidence might have implications for the type of treatment necessary in order for vitamin D screening to be effective. However, the evidence was insufficient to allow conclusions:

- Metaregression analysis in 3 systematic reviews representing a wide range of vitamin D supplementation doses found no differential effect on musculoskeletal health according to vitamin D dose in adults (Chung et al., 2011; Murad et al., 2011) or children and adolescents (Winzenberg et al., 2011). However, the pattern of results across studies of nonskeletal outcomes in the individual trials reviewed for this evidence report sometimes suggested stronger effects from higher doses.
- One systematic review found no connection between adherence and supplementation effect on fall prevention in adults (Murad et al., 2011) and 1 systematic review reported a trend toward greater supplementation effect in prepubertal children who were adherent (Winzenberg et al., 2011). One analysis of the WHI trial detected no differential supplementation effect on all-cause mortality according to adherence (Brunner et al., 2011). The analysis of the WHI trial by LaCroix et al. (2008) suggested a benefit with regard to total mortality for adherent women but not for nonadherent women < 70 years of age.
- A meta-analysis of vitamin D and mortality in unselected adult populations (50 RCTs) found a significant effect overall, but in subgroup analysis according to type of vitamin D only vitamin D3 had a significant effect (Bjelakovic et al., 2011). Bjelakovic and colleagues reported that vitamin D2 and active analogs did not have a significant effect.
- A meta-analysis assessing the effect of vitamin D supplementation on risk of falls reported a significant effect overall but a nonsignificant pooled estimate from studies where vitamin D was not combined with calcium (Murad et al., 2011).

Summary: Differential Effectiveness and Safety of Vitamin D Screening in Healthy Populations (Key Question #4a)

The RCTs selected for evidence of the effectiveness of vitamin D supplementation and *potential* clinical utility of vitamin D testing also served as evidence of differential effectiveness and safety. For evidence pertaining to both musculoskeletal and nonskeletal outcomes, available data on baseline serum levels indicated that a substantial proportion of study groups did not have sufficient serum levels; most study populations represented a range of deficient, insufficient, and sufficient values.

Older adults (low- -quality evidence):

Metaregression Analysis in Systematic Reviews

Differential effect of supplementation on falls according to baseline serum levels depends on setting (lowquality). A systematic review that included studies conducted in all settings detected a substantial difference between data pertaining to subpopulations with known or presumed vitamin D deficiency (odds ratio [OR], 0.53; 95% confidence interval [CI], 0.39 to 0.72) and data pertaining to individuals without evidence of deficiency (OR, 0.90; 95% CI, 0.81 to 0.99). However, for some studies, an assumption of vitamin D deficiency was made only on the basis of risk factors. A systematic review of

supplementation in community-dwelling older adults detected no differential effect by baseline levels of serum 25-OHD on falls.
Differential effect of supplementation on nonvertebral fractures by baseline serum levels (low quality).
The most recent systematic review on vitamin D and fractures included a meta-analysis showing a statistically significant treatment benefit only in individuals with baseline serum 25-OHD levels > 43 nmol/L. No pooled analysis of differential effect on vertebral fractures was possible.

No differential effect of supplementation on falls by sex, age, or other baseline risk factors (low quality).

Subgroup or Regression Analyses Within a Trial
Generally, no differential effect of supplementation, or unclear effect, on numerous outcomes in postmenopausal women (low-quality evidence).
Numerous analyses of a single, very large, good-quality trial with 7-year follow-up detected no differential effect of vitamin D supplementation on risk of fracture, weight control, risk of various forms of cancer or CVD and related mortality, risk of diabetes, or all-cause mortality). Data were available pertaining to the interaction of treatment with all of the patient-related factors of interest specified in the Key Question. There was some suggestion of a differential effect according to baseline serum levels of 25-OHD for CRC, hypertension, and all-cause mortality, but the direction of trends was contradictory across outcomes and no stratum-specific effects were detected. A single small RCT also found no differential effect on mental health measures according to baseline serum 25-OHD.
Exception: Positive effects on risk of fracture in postmenopausal women only in those with a history of ≥ 3 fractures (very–low-quality evidence).

Children and adolescents (metaregression analysis; low-quality evidence):

Uncertain differential effect of supplementation on BMD by baseline serum levels (low-quality evidence).
No differential effect of supplementation on BMD by age (low-quality evidence).

Insufficient evidence:

Differential safety of supplementation for any population.
Differential effectiveness according to testing parameters for any population.
Differential effectiveness according to any factor in younger adults, pregnant women, or lactating women.
Differential effectiveness for prevention of obesity, multiple sclerosis (MS), or depression and mood disorders.

Quality and relevance of the available evidence

The conflicting evidence regarding a differential effect on falls in older adults according to vitamin D status may be explained by more frail study participants in the review with positive results, as well as the authors' assumption that populations with ≥ 2 risk factors for low serum 25-OHD actually were vitamin D deficient. The seemingly contradictory findings of greater reduction in falls in vitamin D-*deficient* individuals but greater reduction in fractures in vitamin D-*sufficient* individuals are difficult to reconcile. The data on subgroup effects on musculoskeletal health were derived from metaregression analysis, which is subject to ecological bias (Murad et al., 2011). In other words, observed relationships between the studies characterized by a mean value for a particular patient factor and the studies reporting a particular treatment effect, does not necessarily mean that the relationship exists in

individuals. The results are heavily influenced by the very large WHI trial, from which a case-control sample indicated a much larger than typical proportion of women with vitamin D insufficiency at baseline. It is possible that the differential effects of supplementation on some outcomes might be detected in large populations representing a wider range of vitamin D status. Evidence pertaining to nonskeletal outcomes came from a single trial, which was a generally good-quality trial, but the follow-up interval might not have been sufficiently long to capture differential effects on mortality or some forms of cancer. Other trials corroborating the results from this trial have not been published. Furthermore, all of the trial participants were postmenopausal women; the results might not be generalizable to men or younger adults. The overall body of evidence concerning a differential effect by patient characteristics is of low quality.

Implications for vitamin D screening

Musculoskeletal Benefits: Evidence pertaining to differential effects does not support a clear role for vitamin D screening to improve musculoskeletal outcomes. Supplementation in older adults has been shown to be helpful for preventing falls, especially in subpopulations with known or suspected vitamin D deficiency, but the evidence does not permit a distinction between the effect of supplementation in older adults with risk factors for vitamin D deficiency and the effect in older adults who have known deficiency based on serum measurements. Other evidence showing that supplementation is effective in community-dwelling older adults, but that effectiveness does not vary according to baseline serum levels in this subpopulation, suggests that screening would not have utility in community-dwelling older adults. There is some evidence that in an overall population of older adults (institutionalized and community-dwelling), the effectiveness of supplementation on falls and fractures varies by baseline vitamin D status, but the trends are in opposite directions for the two outcomes. Other patient characteristics do not appear to be helpful in identifying subpopulations of older adults likely to have the greatest benefit from increased intake; thus, patient factors other than serum levels are not helpful in selecting older adults for screening. For adolescents and children, the evidence, to date, does not suggest that the musculoskeletal benefits of increased intake are dependent on baseline serum levels, and thus the utility of vitamin D screening is questionable in these populations. Nonskeletal Benefits: Evidence to date applies only to postmenopausal women, is derived from a single trial, and has not proven differential nonskeletal benefits according to baseline serum 25-OHD levels or any other patient characteristics. There was some very–low-quality evidence suggesting variable effects across different strata of baseline serum 25-OHD, but trends for different outcomes were contradictory. Thus, vitamin D screening in postmenopausal women would have to be outcome-specific and the utility of screening in other populations is unknown.

Key Question #4b: What is the evidence of the differential clinical utility of vitamin D testing, considering the risk of low serum concentrations and clinical impact of supplementation doses in patients who *already have chronic disease*?

NOTE: Although the key question refers to *testing*, *screening* is a more appropriate term since the implied target populations are generally unselected, i.e., *not* identified on the basis of signs or symptoms of vitamin D insufficiency. The exception is vitamin D and known or suspected osteoporosis.

The RCTs and systematic reviews selected for evidence of the effectiveness of vitamin D supplementation and the potential clinical utility of vitamin D testing in disease populations also served

as evidence of differential effectiveness and safety. None of the selected systematic reviews discussed effectiveness by patient factors.

Findings

Patient Characteristics

Age: As reported by Hayes (2012), a trial of vitamin D3 plus calcium detected only small effects on BMD of the lumbar spine in the overall study group but a pronounced improvement in patients ≤ 70 years of age and a deterioration in patients > 70 years of age.

Baseline Obesity: One of the analyses of the WHI, an RCT (n=36,184) that randomized postmenopausal women to vitamin D (400 IU) plus calcium or placebo and followed them for 7 years, provided data pertinent to the effect of vitamin D supplementation on weight-related outcomes (Caan et al., 2007). Among women who were obese at baseline (BMI ≥ 30 kg/m^2), those who were morbidly obese (BMI ≥ 35 kg/m^2) experienced slightly less mean weight reduction (–0.17 kg) than did women in the obese category (BMI 30 to < 35 kg/m^2; mean –0.23 kg loss), but overlapping CIs for the two estimates of weight loss indicated nonsignificance. In another trial (n=176) that enrolled overweight women, the differences in body weight change between women randomized to orange juice with and without calcium and vitamin D fortification remained nonsignificant after adjusting for baseline total abdominal fat (Rosenblum et al., 2012).

Dietary Intake: A small fair-quality trial detected a significantly greater reduction in body weight and BMI in overweight or obese women who were very low calcium consumers compared with the rest of the study group (Major et al., 2009).

Baseline Serum 25-OHD Level: Another trial (n=438) that enrolled overweight women demonstrated no differences in oral glucose tolerance test results or in blood pressure at 1-year follow-up, either in the overall study group, or in the subgroup with low (< 45 nmol/L) baseline serum 25-OHD (Jorde et al., 2010).

The authors of systematic reviews of RCTs involving individuals with hypertension (Witham et al., 2009) and abnormal glucose (George et al., 2012) noted that the number of studies was too low to allow metaregression analysis of the relationships between the treatment effect and the baseline serum 25-OHD level. However, in 11 studies of patients with abnormal blood glucose, there were consistent results showing a positive effect on glycemic control even though mean baseline serum 25-OHD values ranged from 20 to 95 nmol/L (the threshold considered by the Institute of Medicine [IOM]) to denote sufficiency for optimal bone health is 50 nmol/L). Moderate-quality evidence from 9 RCTs conducted in patients with cardiovascular disease was positive for the effect of supplementation; where reported, mean baseline serum levels were relatively low (25 to 48 nmol/L (see Findings for Key Question #2b.)

Among three RCTs assessing the impact of vitamin D or vitamin D plus calcium on health outcomes in MS patients, conflicting results cannot be explained by baseline serum 25-OHD values. Baseline 25-OHD was high (mean, 73 nmol/L) in the study with positive findings (Burton et al., 2010) but negative in a study conducted in a vitamin D-deficient (25 nmol/L) population (Mosayebi et al., 2011). The third study did not report mean baseline values but excluded patients with serum 25-OHD values ≥ 85 nmol/L (Soilu-Hänninen et al., 2012).

Testing Parameters

No studies directly evaluated the effectiveness of testing. Therefore, the differential effectiveness and safety by type of assay, frequency of monitoring, and time of year that tests are conducted could not be directly evaluated.

Treatment Parameters

Indirect evidence from supplementation trials was considered for insight into treatment factors that might be associated with improvement in outcomes. Such evidence might have implications for the type of treatment necessary in order for vitamin D testing or screening to be effective. However, the only reported finding was a subgroup analysis in a meta-analysis of trials enrolling individuals with hypertension (Witham et al., 2009). Nonsignificant results suggested that vitamin D2 or D3 was more likely than active vitamin D to have an effect on systolic blood pressure.

Summary: Differential Effectiveness and Safety of Vitamin D Screening or Testing in Populations with Chronic Disease (Key Question #4b)

The RCTs and systematic reviews selected for evidence of the effectiveness of vitamin D supplementation and *potential* utility of vitamin D screening/testing in populations with chronic disease were reviewed for evidence of differential effectiveness and safety.

No differential effect of supplementation on glycemic control in adults at high glycemic risk according to baseline serum 25-OHD (low-quality evidence)

Analyses in 1 trial evaluating the effect on the oral glucose tolerance test in obese women and the pattern of results in 11 trials evaluating the effect on glycemic control in adults with abnormal glucose control suggested no differential effects according to baseline serum 25-OHD.

Insufficient evidence of the effect of supplementation on other outcomes or according to other factors

There was no evidence pertaining to the differential effectiveness of vitamin D supplementation with regard to sex, ethnicity/race, geographic location, lifestyle factors, or baseline disease-related risk. There were data from single trials pertaining to effectiveness according to age, baseline obesity (nonsignificant interaction) and baseline intake of calcium (significantly positive for interaction). No trials addressed the issue of differential safety, and there was no evidence pertaining to differential effectiveness according to testing parameters.

Implications for vitamin D screening

Overall, the evidence is insufficient to allow conclusions about either the differential effectiveness and safety of supplementation or the potential utility of vitamin D screening/testing for most outcomes, but low-quality evidence suggesting no differential effect on glycemic control according to baseline serum levels of 25-OHD suggests that vitamin D screening would not have utility for assessing the need to address this particular outcome with supplementation.

Key Question #5: What are the cost implications of vitamin D testing, including the cost-effectiveness of testing compared with not testing?

One poor-quality cost analysis of vitamin D testing was identified, but no cost-effectiveness studies of vitamin D screening or testing were identified. Seven studies evaluating the cost-effectiveness of vitamin D supplementation for prevention of fractures and/or falls were identified. Absolute cost information came from an informal search of the Internet. Details from the 4 selected studies appear in Appendix VI. Four cost-effectiveness studies were excluded because of somewhat serious limitations in the assumption about prevalence or the basis of the effectiveness estimate; see Appendix VII.

Findings

Cost Implications of Vitamin D Testing

Review articles describe vitamin D testing as expensive, especially when patients are found to be deficient and require follow-up tests (Kennel et al., 2010; Kakulavarum and Moore, 2011). Consumer-oriented websites suggest that vitamin D testing at a physician's office could result in a charge of up to $250 if the provider does not do vitamin D testing in house. There are online commercial laboratories that charge in the range of $59 to $69 for a vitamin D (25-OHD) test kit that consumers can take to their healthcare provider for the blood draw.

Vitamin D supplements, on the other hand, at doses recommended by the IOM, are readily available without prescription and are relatively inexpensive. For example, a 3- month supply of vitamin D supplements at 800 IU/day (highest dose recommended by the IOM for healthy adults) costs < $10 (< $40 per year), according to online distributors. Cost-effectiveness studies from a Canadian payer perspective have assumed annual costs of $41 to $86 (USD) for supplying vitamin D supplements to older adults (Singh et al., 2004; Gajic-Veljanoski et al., 2012). Very high dose vitamin D supplements are also available without prescription, although warnings advise against use without consulting a physician. A consumer website advertizes 50,000 IU caps at a price of $19 for a 3-month supply at 1 cap per week (< $80 for a year). The studies reviewed for this report indicated that supplementation is sometimes administered by injection and sometimes at annual doses as high as 600,000 IU; no cost data for these kinds of regimens was found. The literature did not provide guidance as to when mega-dose injections would be preferred; it is possible that the intent of this approach is to assure adherence.

Active forms of vitamin D (calcitriol and synthetic analogs) are often used in patients who have osteoporosis or evidence of poor musculoskeletal health, and some evidence supports the use of active forms over vitamin D2 or D3 (Hayes, 2012). Active vitamin D was also used in several of the studies of patients with abnormal blood glucose that were selected for this evidence report. Consumer prices for a month supply of calcitriol at 0.5 micrograms per day (µg/day) are in the range of $40 per month. Active vitamin D, also sometimes called pharmaceutical vitamin D, requires a prescription and is more expensive than over-the-counter products.

A poor-quality cost analysis based on a retrospective chart review suggested that, assuming at least one routine vitamin D test, subsequent monitoring of serum vitamin D levels could reduce medical costs from the perspective of Veterans Administration (VA) Medical Centers (Bailey et al., 2012). Data for 15,340 patients seen at 6 VA centers were collected. Total outpatient and total inpatient costs were analyzed according to the number of follow-up tests after an initial vitamin D test, vitamin D sufficiency

at the time of initial test, the latitude and season of initial blood draw, and site. Both inpatient and outpatient costs over a 1-year time frame following blood draw were lower in individuals who had sufficient serum vitamin D levels at initial testing and thus no need for monitoring than they were in individuals who tested as vitamin D deficient. However, inpatient and outpatient costs were lower in patients who had ≥ 2 follow-up tests, compared with no follow-up or 1 follow-up test. All factors were statistically significant explanations of cost variation. Lack of data on initial test results, the distribution of vitamin D-replete and vitamin D-deficient individuals who had no follow-up test, disease prevalence and severity, and prescribed supplementation regimens makes these findings difficult to interpret. Furthermore, there was no comparison of costs between individuals who had no vitamin D testing at all and those who had ≥ 1 test.

Cost-Effectiveness of Supplementation

The three selected cost-effectiveness studies evaluated vitamin D supplementation in different older adult populations, generally from a payer perspective (Willis, 2002; Lilliu et al., 2003; Gajic-Veljanoski et al., 2012). All three studies assumed that individuals would receive 800 IU/day of vitamin D3 combined with calcium.

- Gajic-Veljanoski et al. (2012) demonstrated that supplementation in a population of 50-year-old postmenopausal women could reduce the direct medical costs associated with fracture; lifetime cost savings were estimated to be $4196 to $4283 in 2009 US dollars per woman, taking into account long-term care. As noted in Appendix VI, there are some concerns that suggest the effectiveness estimate may be somewhat biased in favor of the cost-savings finding.
- Lilliu et al. (2003) found supplementation to be cost saving for prevention of hip fracture in institutionalized women. Their analysis used data from seven European countries to estimate costs associated with treating a hip fracture. The results suggested total savings of $87,137 to $784,233 per 1000 women (assumed to be 2003 dollars), depending on how costs were reported and the follow-up interval (≤ 1 year postfracture). The cost savings reported by Lilliu and colleagues are imprecise because of the variable manner in which costs were reported by different countries.
- Singh et al. (2004) considered vitamin D and calcium supplementation to be standard care and conducted a study of the cost utility of hip protectors for elderly nursing home residents. Hip protectors were found to be cost saving in comparison with supplementation. The source of the effectiveness estimate for supplementation was a study conducted in women, and the analysis by Singh et al. applied to both men and women.

Summary: Cost and Cost Implications of Vitamin D Testing (Key Question #5)

A single vitamin D test could cost a payer or a consumer more than supplementation for a year with over-the-counter vitamin D2 or D3 at doses recommended by the IOM and, depending on the duration of therapy, testing with follow-up monitoring might likewise exceed the cost of supplementation with active (pharmaceutical) vitamin D. There is evidence from three cost-effectiveness studies in Canada and Europe that routine supplementation with vitamin D3 in postmenopausal or institutionalized women can reduce lifetime costs associates with hip fracture or the cost of treating hip fractures.

Quality and relevance of the evidence

The cost-effectiveness studies were generally well designed. The evidence was considered to be of moderate quality for the limited indication that was addressed. However, the selected studies did not consider vitamin D testing to be one of the costs associated with supplementation. Furthermore, since no trials have assessed the effectiveness of vitamin D testing itself, a cost-effectiveness analysis of vitamin D testing is not possible.

Implications for vitamin D screening

Consistent evidence suggesting that routine supplementation in older populations reduces costs associated with hip fracture also suggests that there is no need for vitamin D screening to identify subpopulations in whom there is a potential for such cost savings. For other populations and outcomes, there is no evidence pertaining to the cost implications of vitamin D testing or screening.

Evidence Pertaining to Indications Outside the PICO Statement

Some chronic disease outcomes and populations were omitted from this report in order to keep the scope manageable. These include allergy, autoimmune disorders other than MS, infectious disease, neurological disease, and chronic pain. The volume of literature is relatively smaller for these disease areas than it is for the populations and outcomes included in the PICO statement. No systematic reviews assessing supplementation and prevention of these types of disease were identified and only a very small number of related observational studies or trials were identified by the 2009 AHRQ report that covered nonskeletal outcomes (Chung et al., 2009). We identified few trials assessing these types of outcomes in healthy populations in our search for RCTs published since 2008. Four systematic reviews in populations *with* a diagnosis related to these omitted areas were identified. They were all Cochrane Reviews and addressed micronutrient supplementation in individuals with human immunodeficiency virus (HIV) infection (2 trials) (Irlam et al., 2010), vitamin D supplementation in adults with chronic pain (4 trials) (Straube et al., 2010), dietary supplementation in individuals with eczema (11 trials, not restricted to vitamin D) (Bath-Hextall et al., 2012), and vitamin D supplementation for cystic fibrosis (3 trials) (Ferguson and Chang, 2012). These reviews found that the evidence pertaining to the effectiveness of vitamin D supplementation was insufficient to allow conclusions.

PRACTICE GUIDELINES AND PUBLIC HEALTH POLICIES

Twenty-six guidelines related to vitamin D testing or supplementation were reviewed. Of these, 17 guidelines with recommendations relevant to the populations defined for this evidence report were assessed for quality and are summarized in Table 1. The titles of these 17 guidelines are underscored in the following discussion. Quality was assessed using the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument (AGREE Enterprise, 2012).

American Academy of Pediatrics (AAP)

In its updated policy, *Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents (good quality)* the AAP recommends that healthy infants, children, and adolescents receive vitamin D at 400 international units per day (IU/day). No recommendations regarding screening were made. These specifics regarding supplementation were recommended (Wagner and Greer, 2008):

- Breastfed and partially breastfed infants should be supplemented with 400 IU/day beginning in the first few days of life.
- All non-breastfed infants and older children who ingest < 1000 mL/day of vitamin D-fortified milk should be supplemented with 400 IU/day.
- All adolescents who do not ingest 400 IU/day through fortified milk and foods should be supplemented with 400 IU/day.
- Children who are at an increased risk of vitamin D deficiency, such as those with malabsorption disorders or use of certain medications, may need higher doses of vitamin D supplementation. Serum 25-hydroxyvitamin D (25-OHD) levels should be checked at 3-month intervals until normal levels have been achieved.
- Infants and children should have serum 25-OHD levels ≥ 50 nanomoles per liter (nmol/L).

The AAP published a clinical report, *Bone Densitometry in Children and Adolescents (good quality)*, which was derived from consensus statements generated at the 2007 Pediatric Position Development Conference of the International Society of Clinical Densitometry (Bachrach and Sills, 2011). Bone densitometry is conducted on children at greatest risk of fragility fractures, including those with recurrent fractures, bone pain, bone deformities, osteopenia, cystic fibrosis, and cancer. The AAP recommends that serum 25-OHD concentrations be measured in children with skeletal fragility to ensure that adequate stores are present.

American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery

In *Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient*, supplementation with vitamin D is recommended for all patients who have undergone gastric bypass surgery to counteract the depletion of fat-soluble vitamins, including vitamin D (Mechanick et al., 2008). Testing for 25-OHD is recommended after malabsorptive bariatric surgery (grade D evidence). Routine supplementation with 400 to 800 U/day vitamin D is recommended. Severe vitamin D malabsorption should be treated with 50,000 to 150,000 U/day vitamin D2 or D3 (grade D evidence). Treatment with vitamin D2 is recommended to prevent secondary hyperparathyroidism (grade C evidence).

American Congress of Obstetricians (ACOG)

An opinion statement by the Committee on Obstetric Practice regarding *Vitamin D – Screening and Supplementation During Pregnancy (very poor quality)* states that current evidence is insufficient to support a recommendation to screen all pregnant women for vitamin D deficiency but advises that serum 25-OHD levels might be tested in pregnant women considered to be at an increased risk of deficiency. *Increased risk* is undefined in the recommendation statement, but vegetarian diet, inadequate sun exposure, and dark skin are listed as risk factors in the background section. Supplementation by 1000 to 2000 IU/day is advised for women who are vitamin D deficient (ACOG, 2011b).

A Practice Bulletin on *Gynecologic Management of Women with Human Immunodeficiency Virus* states that data regarding treatment of osteoporosis in women with HIV infection are lacking but that standard supplementation with calcium and vitamin D is reasonable (ACOG, 2010).

These two statements were not characterized as evidence-based practice guidelines or as reflecting a systematic literature review.

American Medical Directors Association (AMDA)

The AMDA is a national organization comprised of medical directors, attending physicians, and other practitioners who care for patients in the long-term care setting. AMDA produces clinical practice guidelines through interdisciplinary workgroups using both medical evidence and medical consensus. In *Osteoporosis and Fracture Prevention in the Long-Term Care Setting (fair quality)*, the AMDA stated that most institutionalized elderly persons cannot meet calcium and vitamin D requirements through diet alone; therefore, supplementation is suggested for all patients who can tolerate it (AMDA, 2009). Long-term care patients should receive 800 to 1000 IU/day of vitamin D3 or 50,000 IU monthly. Patients with end-stage renal disease may use calcitriol, but calcitriol should be avoided in other patients because of the kidney toxicity associated with this medication. AMDA considers serum 25-OHD testing to be an appropriate companion test with serum calcium, creatinine, and alkaline phosphatase testing in patients who have a history of fracture. AMDA stated that it may be advisable to measure 25-OHD levels in patients who are at risk for osteoporosis and for those with a diagnosis of osteoporosis to help to determine the etiology of the condition.

The Endocrine Society

A Task Force of The Endocrine Society commissioned two systematic reviews of the literature to obtain information regarding vitamin D deficiency. The resulting guideline, *Clinical Practice Guideline for Evaluation, Treatment, and Prevention of Vitamin D Deficiency (good quality)*, which was published in 2011, was created via a consensus process involving the Task Force as well as committees, sponsors, and members of The Endocrine Society (Endocrine Society, 2011). The following recommendations were made:

1. Individuals who are at risk of vitamin D deficiency should be screened, but population screening of individuals who are not at risk of deficiency is not recommended (1; high-quality evidence). (Risk is not defined in the recommendation. Inadequate sun exposure, skin pigmentation, high body mass index [BMI], renal disease, and vitamin D-depleting medication are discussed in the background section.)

2. Measurement of serum circulating 25-OHD by a reliable assay is the recommended method to screen individuals at risk of vitamin D deficiency. The serum 1,24-dihydroxyvitamin D assay is not recommended for this purpose (1; high-quality evidence).

3. The following vitamin D dietary intake recommendations were made for patients who are at risk of vitamin D deficiency:

    - Age 0 to 1 year: 400 IU/day (2; high-quality evidence).
    - Age > 1 year to 70 years: ≥600 IU/day (2; high-quality evidence).
    - Age > 70 years: 800 IU/day (2; high-quality evidence).
    - Pregnant and lactating women: ≥ 600 IU/day (2; moderate-quality evidence).
    - Obese children and adults, 2 to 3 times the suggested dose for their age group (2; high-quality evidence).

- Children and adults taking anticonvulsants, glucocorticoids, antifungals, or acquired immunodeficiency syndrome medications: 2 to 3 times the suggested dose for their age group (2; high-quality evidence).

The Task Force acknowledges that it is unknown whether these doses of vitamin D are sufficient to provide health benefits.

4. The Task Force recommends vitamin D2 or vitamin D3 to prevent or treat vitamin D deficiency. The following recommendations were made for patients who have vitamin D deficiency (2; high-quality evidence):

    - Age 0 to 1 year: 2000 IU/day or 50,000 IU/week for 6 weeks.
    - Age 1 year to 18 years: 2000 IU/day or 50,000 IU/week for ≥ 6 weeks.
    - Adults: 6000 IU/day or 50,000 IU/week for 8 weeks.
    - Individuals who are obese, have malabsorption syndromes, or are on medications affecting vitamin D metabolism: 6000 to 10,000 IU/day.

5. Vitamin D supplementation is recommended for fall prevention. Vitamin D supplementation is not recommended for the purpose of preventing cardiovascular disease or death or improving quality of life (2; high-quality evidence).

The Endocrine Society grades the quality of the evidence and the strength of the recommendation. Strong recommendations are designated with a "1" and weak recommendations are designated with a "2." The quality of the evidence is rated as 1 of 4 levels, ranging from "very low" to "high."

Institute for Clinical Systems Improvement (ICSI)

The ICSI guideline on *Diagnosis and Treatment of Osteoporosis (good quality)* lists vitamin D deficiency as a risk factor for developing osteoporosis (ICSI, 2011a). ICSI recommends that serum 25-OHD levels be determined for all patients with osteoporosis (ungraded recommendation) with the optimum defined as ≥ 30 nanograms per milliliter (ng/mL) (75 nmol/L) to maximally suppress parathyroid hormone secretion. Patients with osteoporosis need to have adequate vitamin D stores prior to initiation of pharmacologic osteoporosis therapy. ICSI also recommends that patients be informed of the importance of adequate vitamin D levels for the prevention of osteoporosis.

The *Routine Prenatal Care (good quality)* guideline states that there was no clinical evidence of a benefit from universal supplementation with a multivitamin before conception or during pregnancy (Evidence Grade A) (ICSI, 2010). Vitamin D supplementation of 400 IU/day during pregnancy is recommended for women who are absolute vegetarians and those who do not consume vitamin D fortified milk.

The *Prevention and Management of Obesity (Mature Adolescents and Adults)* guideline recommends that patients receiving orlistat supplement their diet with a multivitamin to counteract the depletion of fat-soluble vitamins, including vitamin D, in patients taking orlistat (ICSI, 2011b). Patients who have undergone gastric bypass surgery have a limited ability to absorb nutrients; therefore, ICSI recommends supplementation with 400 to 800 milligrams (mg) calcium citrate with added vitamin D twice daily. When given alone, the recommended dose of vitamin D supplementation is 600 to 50,000 IU/day.

The *Preventive Services for Children and Adolescents (good quality)* guideline recommends that mothers of breastfed infants be encouraged to start infant supplementation with 400 IU/day vitamin D beginning within 2 months of age (low-quality evidence) (ICSI, 2011c).

The ICSI grades evidence based on the source of the data. In 2011, ICSI began transitioning to a new grading system. Before 2011, evidence graded as Class A was derived from randomized controlled trials (RCTs). Guidelines published in 2011 and later grade the evidence as high, moderate, or low. Low-quality evidence means the estimate of effect is uncertain based on the available research data.

Medical Advisory Secretariat (MAS), Ministry of Health and Long-Term Care, Ontario

A report on *Clinical Utility of Vitamin D Testing (fair quality)* concluded that vitamin D testing was not warranted for the average-risk population. *Average risk* was not defined, but the rationale for this conclusion included the lack of precise target serum levels and the lack of clear supplementation guidelines from Health Canada. The report relied heavily on two reports by the Agency for Healthcare Research and Quality (AHRQ) (Cranney et al., 2007; Chung et al., 2009) cited in the current evidence review. The report also concluded that individuals with renal or liver disease, osteoporosis, malabsorption syndromes, or conditions requiring medications that can affect vitamin D absorption/metabolism should follow physician guidance regarding testing as well as supplementation. The report acknowledges that there is no moderate- or high-quality evidence demonstrating an effect on nonskeletal health outcomes, even in patients with chronic kidney disease, but does not state an explicit recommendation concerning testing or supplementation in patients with the disease indications (e.g., cancer, cardiovascular disease) targeted in the current evidence report (MAS, 2010).

National Institute for Health and Clinical Excellence (NICE)

NICE develops guidances using its public health program process. The guidances represent the views of NICE and are developed after careful consideration of the available evidence.

Guidelines for improving the nutrition of pregnant and breastfeeding mothers and children in low-income households were prepared in 2008 and amended in 2011 (NICE, 2011a). The *Maternal and Child Nutrition (good quality)* guidance has recommendations directed at healthcare providers, healthcare commissioners and mangers, and public- and private-sector organizations. The following are key recommendations from the guidance: (1) women who are pregnant or may become pregnant should take maternal vitamin supplements that include vitamin D; (2) pregnant women should be advised about the benefits of vitamin D supplementation during pregnancy and breastfeeding; (3) clinicians should especially insure that women who are most at risk of deficiency (limited exposure to sunlight; South Asian, African, Caribbean, or Middle Eastern descent; obese) are following supplementation advice; and (4) vitamin supplements should be offered to children aged 6 months to 4 years. There is a need for research into the acceptability of dietary and lifestyle interventions to improve the vitamin D status of mothers and children aged ≤ 5 years, particularly those from vulnerable groups.

In 2010, NICE updated a 2008 guideline for the care of healthy pregnant women, *Antenatal Care: Routine Care for the Healthy Pregnant Woman (good quality)* (NICE, 2010). The guideline was developed by the National Collaborating Centre for Women's and Children's Health who consulted with healthcare professionals to review the evidence and generate recommendations. All pregnant women should be advised of the importance of vitamin D for their own and their baby's health. Pregnant women may take 10 µg of vitamin D each day as part of a multivitamin. Women at risk of vitamin D deficiency include

those who are of South Asian, African, Caribbean, or Middle Eastern descent; have limited exposure to sunlight; have a diet particularly low in vitamin D; or a pre-pregnancy body mass index > 30 kg/m^2. Healthcare professionals need to insure that these women, in particular, are taking vitamin D supplementation. There is a need for research into the effectiveness of routine vitamin D supplementation for pregnant and breastfeeding women.

The NICE guidance *Chronic Kidney Disease: Early Identification and Management of Chronic Kidney Disease in Adults in Primary and Secondary Care* was also developed by the National Collaborating Centre for Chronic Conditions (NICE, 2008). Individuals with chronic kidney disease may develop osteoporosis and bone metabolism complications. NICE does not recommend routine measurement of vitamin D levels in individuals with stage I, 2, 3A, or 3B chronic kidney disease. When vitamin D supplementation is indicated, individuals with stage 1, 2, 3A, or 3B disease should receive vitamin D3 or D2 and those in stage 4 or 5 disease should receive alfacalcidiol or calcitriol (active forms of vitamin D). NICE guidance on *Cinacalcet for the Treatment of Secondary Hyperparathyroidism in Patients with End-Stage Renal Disease on Maintenance Dialysis Therapy* guidance identifies active forms of vitamin D (calcitriol, alfacalcidiol, paricalcitol) as part of the treatment regimen for secondary hyperparathyroidism. (NICE, 2007). These indications are not among the target indications for the current evidence report.

The NICE guidelines for preventing falls in elderly people are presented in *Falls: The Assessment and Prevention of Falls in Older People (good quality)* (NICE, 2004). There is emerging evidence that correction of vitamin D deficiency or insufficiency may reduce the propensity for falling and that the use of calcium and vitamin D therapy reduces the rate of fracture in elderly people. However, according to the evidence reviewed for this guideline, uncertainty remains about whether vitamin D might reduce fracture by reducing the propensity to fall or by improving bone mass effective doses and routes of administration have not been established. Therefore, NICE does not recommend supplementation with vitamin D as a preventive measure against falls.
NICE prepared two guidelines for treatments of osteoporosis entitled *Alendronate, Etidronate, Risedronate, Raloxifene, Strontium Ranelate and Teriparatide for the Secondary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women (good quality)* (NICE, 2011b) and *Alendronate, Etidronate, Risedronate, Raloxifene, Strontium Ranelate and Teriparatide for the Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women (good quality)* (NICE, 2011c). NICE recognized that adequate levels of calcium and vitamin D are needed to ensure optimum effects of osteoporosis treatments. Both guidelines assume that women have adequate calcium intake and are vitamin D replete. Neither guideline makes any recommendation concerning testing or monitoring vitamin D status.

In 2012, NICE prepared guidelines for treating individuals with epilepsy entitled *The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care* (NICE, 2012). NICE recommends monitoring vitamin D levels, among other tests of bone metabolism, every 2 to 5 years for individuals who are receiving enzyme-inducing drugs as part of their epilepsy treatment regimen. This indication is not among the target indications for the current evidence report.

North American Menopause Society

A 2010 position statement from this organization on *Updates on Screening, Prevention and Management of Postmenopausal Osteoporosis (good quality)* acknowledges that the appropriate vitamin D replacement regimen for women with osteoporosis, as well as whether therapy should target

certain serum levels or be defined according to a set dose, are unknown and require further research (Schnatz, 2011).

Osteoporosis Canada

Guidelines on *Vitamin D in Adult Health and Disease (good quality)* were produced in 2010 after a systematic review of the literature (through June 2008) and a consensus process (Hanley et al., 2010). Ten recommendations relative to the link between vitamin D deficiency and osteoporosis; optimal serum levels; laboratory quality; testing, supplementation, and monitoring in different populations; and areas needing further research include:

1. Adequate vitamin D status, in addition to calcium from diet or supplements, is essential for the prevention of osteoporosis (level 1 evidence, grade A recommendation).
2. Administration of vitamin D and calcium should not be used as the sole treatment for osteoporosis (level 1 evidence, grade A recommendation).
3. The optimal level of serum 25-OHD for musculoskeletal benefits is ≥ 75 nmol/L (level 2 evidence, grade B recommendation).
4. Laboratories performing 25-OHD testing should take part in external proficiency surveys and should demonstrate that values reported for shared samples approximate the consensus of values reported by others (level 4 evidence, grade D recommendation).
5. In healthy adults at low risk for vitamin D deficiency (i.e., < 50 years of age, without osteoporosis or conditions affecting vitamin D absorption or action), routine vitamin D supplementation (10 to 25 micrograms [µg] [400 to 1000 IU] daily) is recommended. Serum 25-OHD should not be measured (level 5 evidence, grade D recommendation).
6. Adults > 50 years of age are at moderate risk for vitamin D deficiency. Supplementation with ≥ 20 to 25 µg (800 to 1000 IU) of vitamin D3 daily is recommended. To achieve optimal vitamin D status (> 75 nmol/L), many individuals may require supplementation > 25 µg (1000 IU) daily. Doses ≤ 50 µg (2000 IU) are safe and do not require monitoring (level 3 evidence, grade C recommendation). NOTE: The Institute of Medicine (IOM) has defined adequate vitamin D status as ≥ 50 nmol/L.
7. For individuals receiving pharmacologic therapy for osteoporosis, measurement of serum 25-OHD should follow 3 to 4 months of adequate supplementation and should not be repeated if the optimal level is achieved (grade D recommendation).
8. Measurement of serum 25-OHD is recommended for individuals with recurrent fractures, bone loss despite osteoporosis treatment, or comorbid conditions that affect vitamin D absorption or action (grade D recommendation). Dose requirements above Health Canada's current tolerable upper intake level (50 µg [2000 IU]) may be needed, in which case monitoring of serum 25-OHD levels is required (level 4 evidence, grade D recommendation).
9. Exposure to natural sunlight, when used in moderation (avoiding sunburn) and individualized to the person's skin type, can contribute to summertime vitamin D sufficiency (level 2 evidence, grade B recommendation).
10. Research is needed to better define the minimum required daily dose and the optimal dose for musculoskeletal and other health benefits and to better establish the tolerable upper level for vitamin D supplementation (grade D recommendation).

Osteoporosis Canada grades research evidence according to seven levels ranging from Level 6 (case series without controls) to 1+ (systematic overview of meat-analysis of RCTs). Recommendations are

given 1 of 4 grades (D – lowest, to A – highest) according to the type of supporting evidence that is available.

U.S. Preventive Services Task Force (USPSTF)

A 2003 USPSTF report on *Counseling for Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease* made no recommendations with respect to Vitamin D. The Methods sections of the two evidence summaries for prevention of cancer and prevention of cardiovascular disease indicate that vitamin D was not included in the search strategy (USPSTF, 2003).

In May 2012, the USPSTF issued a final report on *Prevention of Falls in Community-Dwelling Older Adults (good quality)* that evaluated a range of preventive interventions (USPSTF, 2012a). This report was based on a USPSTF systematic review and meta-analysis (Michael et al., 2010), which estimated that vitamin D supplementation reduces the risk of falling by 17% over 6 to 36 months (see Appendix III). Regarding vitamin D supplementation, the report concluded that the harms of vitamin D supplementation are no greater than small, citing the Women's Health Initiative (WHI) trial findings of a small increase in the risk for renal stones. The USPSTF advises the following:

Prevention of falls:

> Vitamin D supplementation in community-dwelling adults aged 65 years or older who are at increased risk for falls (B for moderate certainty of a net benefit).

The most recent evidence report on vitamin D conducted on behalf of the AHRQ (Chung et al., 2011) was designed to support a USPSTF policy on vitamin D. Using the work by Chung et al. as a foundation, the USPSTF has issued a draft report on *Vitamin D and Calcium Supplementation to Prevent Cancer and Osteoporotic Fractures in Adults (good quality).* Four recommendations regarding supplementation have been proposed (USPSTF, 2012b):

Primary prevention of cancer:

> Vitamin D supplementation, with or without calcium, adults (I for insufficient evidence regarding the balance of benefits and harms).

Primary prevention of fractures:

> Combined vitamin D and calcium supplementation, premenopausal women or men (I for insufficient evidence regarding the balance of benefits and harms).
>
> Daily supplementation with > 400 IU/ day of vitamin D3 and 1000 mg of calcium, noninstitutionalized postmenopausal women (I for insufficient evidence regarding the balance of benefits and harms).
>
> Daily supplementation with ≤ 400 IU of vitamin D3 and 1000 mg of calcium carbonate, noninstitutionalized women (D for moderate certainty of no net benefit).

No recommendations regarding testing or monitoring vitamin D status are included in either of the two 2012 reports (USPSTF, 2012a; USPSTF, 2012b).

World Health Organization (WHO)

Three relevant guidelines were identified but were not reviewed in detail and do not appear in Table 1 because they do not apply primarily to North American populations. A Technical Report on *Optimal Feeding of Low-Birth-Weight Infants* (Edmond and Bahl, 2006) advises that increasing the usually recommended doses of 400 IU/day for infants fed unsupplemented human milk offers no benefit for low-birthweight infants. No recommendations regarding screening or testing were found in these documents. A report on *WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia* (WHO, 2011) identified vitamin D supplementation as an intervention that is *not* recommended for prevention of pre-eclampsia and related complications. The Second Edition (2004) of a report on *Vitamin and Mineral Requirements in Human Nutrition* states that conventional vitamin D supplementation during pregnancy should probably not be discouraged but that there is little support for increased supplementation in lactating women (WHO, 2004).

Other Organizations Searched

Websites for the following organizations were searched and no guidelines pertaining to vitamin D were found: American Academy of Family Physicians, American College of Physicians, National Osteoporosis Foundation.

Summary: Guidelines

Seventeen generally good-quality guidelines addressed vitamin D testing and/or supplementation in populations relevant to this report. The guidelines' recommendations for supplementation are consistent with current Institute of Medicine (IOM) recommendations.

Three good-quality guidelines, one fair-quality guideline, and one very–poor-quality guideline recommend against routine screening for vitamin D status: in adults and children (The Endocrine Society; MAS, Ontario; Osteoporosis Canada), in pregnant women (ACOG), and in children (AAP). The Endocrine Society, MAS, and ACOG guidelines also explicitly or implicitly support screening in individuals who are at general high risk, but definitions of high risk are lacking. The guidelines identify general factors such as sun exposure, dark skin, and nutritional intake as risk factors in their background sections. Osteoporosis Canada recommends testing and supplementation in individuals being treated pharmaceutically for osteoporosis and follow-up testing at 3 to 4 months.

These recommendations against routine screening are consistent with the lack of direct evidence that vitamin D testing improves outcomes, as well as the general lack of moderate or high-quality evidence that supplementation improves outcomes in healthy populations. The at-risk populations that some guidelines imply might be appropriate for routine screening are defined, in part, by demographic and lifestyle factors that have a known association with lower serum levels. However, there is no evidence demonstrating that screening or supplementation in groups defined by these factors is more effective than in the general population.

Three fair- to good-quality guidelines recommend testing in populations with known poor bone health: children with skeletal fragility (AAP) and adults with osteoporosis (ICSI, Osteoporosis Canada). These recommendations are weakly supported by evidence of the effectiveness of supplementation in these populations, but there is no direct evidence concerning the clinical utility of testing. The Osteoporosis

Canada guidelines add that monitoring is not necessary at vitamin D doses < 2000 IU/day because such doses are safe but that monitoring every 3 to 4 months until adequate levels are achieved is advised for patients undergoing pharmacologic therapy. Two good-quality guidelines by the National Institute for Clinical and Health Excellence (NICE) on pharmaceutical treatments for primary and secondary prevention of osteoporosis assume that women are vitamin D replete. However, the NICE guidelines do not offer guidance on recommended intake, supplementation, or testing..

Other guidelines recommending vitamin D testing only addressed indications that are outside the PICO-defined scope of this report: CKD, use of obesity medications that cause vitamin D depletion, and history of malabsorptive bariatric surgery. These guidelines were not evaluated for quality.

Table 1. Summary of Practice Guidelines and Public Health Policies

Sponsor, Title	Recommendations Concerning Vitamin D Testing and/or Supplementation in Healthy Populations and Populations with Chronic Disease*	Quality† (7=highest)
ADULTS		
American Medical Directors Association (AMDA); *Osteoporosis and Fracture Prevention in the Long-Term Care Setting.*	• Routine administration of vitamin D3 at 800-1000 IU/day or 50,000 IU/month in long-term care residents.	4-5
The Endocrine Society; *Clinical Practice Guideline for Evaluation, Treatment, and Prevention of Vitamin D Deficiency*	• **Screening only in individuals who are at risk of vitamin D deficiency.** • Recommended dietary vitamin D intake: 18-70 years of age, ≥600 IU/day; >70 years of age, 800 IU/day. • Supplementation with 6000 IU/day or 50,000 IU/week vitamin D to treat vitamin D deficiency. • Obese adults and those taking medications that affect vitamin D metabolism: 6000-10,000 IU/day. • Vitamin D supplementation for fall prevention, not cardiovascular disease prevention.	6
Osteoporosis Canada; *Vitamin D in Adult Health and Disease*	• Routine supplementation (400-1000 IU/day) and **no serum measurements in healthy adults without risk of deficiency** (< 50 years of age, without osteoporosis or conditions affecting vitamin D absorption or action).	6
USPSTF; *Vitamin D and Calcium to Prevent Cancer and Fractures in Adults (draft)*	• Evidence is insufficient for a recommendation concerning prevention of cancer with supplementation. • Evidence is insufficient for a recommendation concerning prevention of fractures in men or premenopausal women with supplementation. • Evidence is insufficient for a recommendation concerning prevention of fractures in noninstitutionalized postmenopausal women at vitamin D doses >400/day. • Moderate certainty of *no benefit* for prevention of fractures in noninstitutionalized women at vitamin D doses ≤400 IU/day.	7
PREGNANT and LACTATING WOMEN		
American Congress of Obstetricians and Gynecologists (ACOG); *Vitamin D – Screening and Supplementation During Pregnancy*	• **Routine screening of pregnant women is *not* recommended.** • **Screening may be considered in pregnant women considered to be at an increased risk of deficiency.** • Vitamin D at 1000-2000 IU/day in vitamin D deficient pregnant women.	1
The Endocrine Society; *Clinical Practice Guideline for Evaluation, Treatment, and Prevention of Vitamin D Deficiency*	• **Screening in individuals who are at risk of vitamin D deficiency.** • **General population screening is *not* recommended.** • Recommended dietary intake: ≥6000 IU/day.	6
ICSI; *Routine Prenatal Care*	• Universal vitamin D supplementation before conception or during pregnancy is *not* recommended. • 400 IU/day vitamin D during pregnancy for women who are absolute vegetarians.	6
NICE; *Antenatal Care: Routine Care for the Healthy Pregnant Woman*	• Pregnant women take 10 µg/day vitamin D as part of a multivitamin. • Healthcare providers need to ensure that women who are at risk of vitamin D deficiency (due to limited sun exposure, race/ethnicity, poor diet, or obesity) are receiving vitamin D supplements.	7

Sponsor, Title	Recommendations Concerning Vitamin D Testing and/or Supplementation in Healthy Populations and Populations with Chronic Disease*	Quality† (7=highest)
NICE; *Maternal and Child Nutrition*	• Women who are, or may become, pregnant should take vitamin D supplements. • Healthcare providers need to ensure that women who are at risk of vitamin D deficiency (due to limited sun exposure, race/ethnicity, or obesity) are receiving vitamin D supplements.	7
CHILDREN		
American Academy of Pediatrics; *Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents*	• Infants and children should have serum 25-OHD levels ≥50 nmol/L. • Infants, children, and adolescents should be supplemented with 400 IU/day vitamin D.	6
The Endocrine Society; *Clinical Practice Guideline for Evaluation, Treatment, and Prevention of Vitamin D Deficiency*	• **Individuals who are at risk of vitamin D deficiency should be screened, general population screening is not recommended.** • Recommended dietary intake: 0-1 year of age, 400 IU/day; >1 year to 17 years of age, ≥600 IU/day. • Obese children and those taking medications that affect vitamin D metabolism: 2 to 3 times recommended daily intake. • Supplementation with 2000 IU/day or 50,000 IU/week vitamin D is recommended to treat vitamin D deficiency.	6
ICSI; *Preventive Services for Children and Adolescents*	• 400 IU/day vitamin D for breastfed infants beginning, to be started within 2 months of age.	6
NICE; *Maternal and Child Nutrition*	• Vitamin supplements, which include vitamin D, should be offered to children of 6 months to 4 years of age who are members of low-income households.	7
ADULTS OR CHILDREN		
Medical Advisory Secretariat, Ministry of Health and Long-Term Care; *Clinical Utility of Vitamin D Testing*	• **Vitamin D testing is not warranted for the average-risk population**. (Individuals with renal or liver disease, osteoporosis, malabsorption syndromes, or conditions requiring medications that can affect vitamin D absorption/metabolism should follow physician guidance regarding testing as well as supplementation.)	4
DISEASE- or RISK–FACTOR-SPECIFIC		
American Academy of Pediatrics; *Bone Densitometry in Children and Adolescents*	• Serum 25-OHD monitoring in children with skeletal fragility to ensure that adequate stores are present.	6
American Medical Directors Association; *Osteoporosis and Fracture Prevention in the Long-Term Care Setting*	• **Serum 25-OHD testing in patients at risk for osteoporosis and also those diagnosed with osteoporosis.**	5
ICSI; *Diagnosis and Management of Osteoporosis*	• **25-OHD testing in patients with osteoporosis (optimum level 75 nmol/L).**	6
NICE; *Falls: The Assessment and Prevention of Falls in Older People*	• Vitamin D supplementation as a preventive measure against falls is *not* recommended	7
NICE; *(1) Secondary Prevention*	• Both guidelines assume that women have adequate calcium intake and are vitamin D replete to ensure optimum effects	7

Sponsor, Title	Recommendations Concerning Vitamin D Testing and/or Supplementation in Healthy Populations and Populations with Chronic Disease*	Quality† (7=highest)
of Osteoporotic Fragility Fractures in Postmenopausal Women; (2) Primary Prevention of Osteoporotic Fragility Fractures in Postmenopausal Women	of osteoporosis treatments.	
North American Menopause Society; *Updates on Screening, Prevention and Management of Postmenopausal Osteoporosis*	• Appropriate vitamin D replacement regimen for women with osteoporosis is unknown. • Target vitamin D serum levels in women with osteoporosis are unknown.	6
Osteoporosis Canada; *Vitamin D in Adult Health and Disease*	• For individuals receiving **pharmacologic therapy for osteoporosis, measurement of serum 25-OHD following 3-4 months of adequate supplementation** and should not be repeated if the optimal level is achieved. • **Serum 25-OHD testing is recommended for individuals with recurrent fractures, bone loss despite osteoporosis treatment**, or comorbid conditions that affect vitamin D absorption or action. • **Doses ≤50 µg (2000 IU) are safe and do not require monitoring.**	6
USPSTF; *Prevention of Falls in Community-Dwelling Older Adults*	• Vitamin D supplementation in community-dwelling adults ≥65 years of age who are at increased risk for falls.	7

*Only guidelines/recommendations pertaining to the populations specified in the PICO statement for this report are listed in the table.
†Quality was assessed according to the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument (AGREE Enterprise, 2012).

SELECTED PAYER POLICIES

At the direction of WA HTA, the coverage policies for the following organizations were reviewed:

Centers for Medicare & Medicaid Services (CMS): No National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) for the State of Washington were identified that pertained to vitamin D testing or supplementation (CMS, 2012).

Aetna: No coverage policy for vitamin D testing was identified on the Aetna website. However, Aetna does cover calcitriol and paricalcitol injections when considered medically necessary for the management of hypocalcemia and/or secondary hyperparathyroidism in members who have chronic renal failure and are undergoing hemodialysis. Aetna considers calcitriol injection experimental and investigational for the treatment of cystic fibrosis, multiple sclerosis, prostate cancer, and other solid tumors/cancers. Aetna considers paricalcitol injection experimental and investigational for the treatment of diabetic nephropathy, myelodysplastic syndrome, pancreatic cancer, and posttransplantation nephropathy. These excluded indications are not considered all-inclusive (Aetna, 2012). (Calcitriol and paricalcitol are active analogs of vitamin D.)

Link to Aetna Policy Number 0022: http://www.aetna.com/cpb/medical/data/1_99/0022.html.

Regence BCBS: According to Regence Group policy, serum 25-hydroxyvitamin D (25-OHD) testing may be medically necessary in patients with a clinically documented underlying disease or condition that is specifically associated with vitamin D deficiency or decreased bone density. Examples include kidney stones, celiac disease, chronic kidney disease, end-stage renal disease, liver disease, hypercalcemia, hyperparathyroidism, osteoporosis, and rickets, among others. Regence Group does not consider 25-OHD testing medically necessary for routine or initial screening in the absence of clinical documentation of an underlying disease or condition specifically associated with vitamin D deficiency. Testing 1,25-(OH)2-D serum levels, according to Regence Group policy, may be medically necessary in the evaluation or treatment of the conditions that may be associated with defects in vitamin D metabolism. Examples include kidney or ureter stones, disorders of calcium metabolism, hyperparathyroidism, hypoparathyroidism, rickets, and sarcoidosis, among others. Testing 1,25-(OH)2-D serum levels is not medically necessary for testing and screening for vitamin D deficiency because this test is not considered a reliable indicator of vitamin D serum levels (Regence Group, 2011).

Link to Regency Policy No. 52: http://blue.regence.com/trgmedpol/lab/lab52.html.

GroupHealth: No coverage policies concerning vitamin D testing or supplementation were identified on the GroupHealth website (GroupHealth, 2012).

Summary of Payer Policies

Neither CMS nor GroupHealth has a policy regarding vitamin D testing or vitamin D supplementation. Aetna covers injections of two forms of active vitamin D (calcitriol and paricalcitol) for treatment of hypocalcemia and/or secondary hyperparathyroidism, but only in individuals undergoing hemodialysis for chronic renal failure. Regence Group covers serum 25-OHD and 1,25-(OH)2-D testing in individuals

who either have a documented disease or condition known to cause vitamin D depletion, e.g., metabolic disorders, or have radiological or laboratory findings that are positive for markers for insufficiency, e.g., osteoporosis or hyperparathyroidism. Except for osteoporosis and rickets, the conditions covered by Regence Group for vitamin D testing are not among the indications of interest that were specified in the PICO statement for this evidence report.

OVERALL SUMMARY AND DISCUSSION

Evidence-Based Conclusions

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. However, for some populations and outcomes, an association between serum levels and health outcomes and/or a positive effect of supplementation on health outcomes has been demonstrated. Thus, vitamin D screening has *potential* utility for identifying individuals who could benefit from the preventive or disease-modifying effects of supplementation in these clinical situations. Both vitamin D screening/testing and vitamin D supplementation are generally safe interventions.

Findings for the Key Questions #1, #2, #4, and #5 are summarized in Table 2, by population and outcome. The table does not explicitly reflect evidence pertaining to Key Question #3 (safety), but safety is taken into account in assigning the overall clinical value of screening/testing.

Indications for Which Vitamin D Screening/Testing Could Possibly Have Value

The first section of Table 2 suggests that there are two areas where information about vitamin D serum levels might have some value: (a) to demonstrate the need for supplementation as a means of reducing disease and mortality risk in postmenopausal women and (b) to inform treatment for individuals with known or highly suspected osteoporosis.

The use of vitamin D screening to assess risk of disease (some forms of cancer and cardiovascular disease) and mortality in postmenopausal women is supported by evidence of an association between serum 25-OHD and these outcomes in adults, by low-quality evidence that supplementation improves these outcomes in older adults, and by low-quality evidence that the effectiveness of supplementation in postmenopausal women, with respect to these outcomes, varies according to baseline serum levels of 25-OHD. Thus, vitamin D screening may have value for determining the need for supplementation to reduce mortality and the risk of cancer and cardiovascular disease in postmenopausal women. However, lack of a definitive cutoff point specific to these outcomes precludes precise clinical decision rules. Clinical application of the available evidence is further complicated by findings suggesting that only individuals with *insufficient* levels of vitamin D benefit from supplementation in terms of cancer risk and all-cause mortality, whereas only individuals with *high* levels of vitamin D benefit in terms of hypertension risk. As shown in the middle and bottom sections of Table 2, there is no evidence that vitamin D screening in postmenopausal women or in any healthy adult population has value for improving any other outcomes. Furthermore, future cost-effectiveness studies could show that routine supplementation *without screening* in postmenopausal women is cost-effective for reducing cancer, cardiovascular, and mortality risk, as has been shown for supplementation without screening to reduce

fractures in older women. The overall quality of the evidence supporting vitamin D screening to reduce health risk in postmenopausal women is thus very low, meaning that our confidence in this conclusion is very weak. There is extremely sparse evidence pertaining to the differential effect of supplementation in adults other than postmenopausal women and thus, the evidence is insufficient for forming conclusions about vitamin D screening to assess health risks in other adult populations.

Vitamin D testing to plan and monitor supplementation with active [pharmaceutical] or high-dose inactive vitamin D in individuals with known or high suspicion of osteoporosis is supported by evidence of an association between serum levels and musculoskeletal health in such populations, moderate-quality evidence of the effectiveness of supplementation with active forms of vitamin D to treat osteoporos, and safety concerns with both active vitamin D and very high doses of inactive vitamin D. The overall quality of the evidence for this conclusion is of moderate quality, meaning that we can have reasonable confidence that the available evidence represents the true value of vitamin D testing for this indication. Although no evidence pertaining to a differential effect of supplementation according to baseline serum levels was identified, osteoporosis is considered an objective marker for insufficient serum levels of vitamin D. Testing to confirm low serum vitamin D before treatment with a pharmaceutical product is reasonable, particularly since the active (pharmaceutical) forms of vitamin D are more likely than inactive vitamin D to produce toxicity. Treatment of osteoporosis could conceivably involve *inactive* vitamin D at doses higher than those considered by the Institute of Medicine to be safe for routine use (4000 IU/day for adults), thus requiring monitoring both to avoid vitamin D toxicity during treatment and to determine when high-dose supplementation can be discontinued. (However, no trials evaluating the effectiveness of megadoses of inactive vitamin D were identified.)

Indications for Which Vitamin D Screening Likely Has No Value

An additional indication for vitamin D screening might be considered reasonable based on the available evidence. That would be screening to assess the need for supplementation to promote musculoskeletal health in adult populations selected only because of older age. There is an association between vitamin D status and bone mineral density (BMD) in this population, as well as a positive effect of vitamin D supplementation on BMD, falls, and fractures. Whether the overall effect on musculoskeletal health differs by baseline vitamin D status is unclear; findings to date are difficult to reconcile. At any rate, since routine supplementation of postmenopausal or institutionalized women *without screening* has been shown to be cost-effective as a preventive treatment for fracture, screening would seem to be an unneeded expense in older women. Since the effect of supplementation was found not to vary by sex, the cost-effectiveness of routine supplementation without screening in men might also be inferred.

Vitamin D screening in healthy adults appears to have no value for reducing the risk of type 2 diabetes. Vitamin D screening in adults with abnormal blood glucose also appears to have no value for improving outcomes related to diabetes. The overall quality of the evidence for these conclusions is low, meaning that we can have little confidence in them and future studies might reverse them.

Indications for Which the Evidence Is Insufficient to Allow Conclusions

There is insufficient evidence to allow conclusions about the value of vitamin D screening in healthy adults to reduce the risk of obesity, depression and mood disorder, or multiple sclerosis (MS); in healthy adults younger than middle age to reduce the risk of any disease or poor health condition; in pregnant or lactating women to improve relevant outcomes; in adults with obesity, cardiovascular disease, cancer, MS, or depression; in healthy pediatric populations to reduce the risk of any disease or poor

health condition or in pediatric populations selected on the basis of the diseases of interest. For these indications, there was no evidence or no consistent and statistically significant evidence pertaining to the differential effect of supplementation according to baseline serum levels. Evidence pertaining to other questions was generally missing, negative, or unclear.

Table 2. Summary of Findings

Key (abbreviations): 25-OHD, 25-hydroxyvitamin D (the circulating form of vitamin D that is usually measured in vitamin D screening/testing); BMC, bone mineral content; BMD, bone mineral density; CVD, cardiovascular disease; MS, multiple sclerosis; QOL, quality of life

Key (symbols):

- ✓ Beneficial association, treatment effect, or clinical value
- **+/–** Inconsistent study findings
- **0** No association, treatment effect, or overall clinical value
- **X** Harmful association or treatment effect
- **I** Insufficient evidence (association with serum 25-OHD: no longitudinal data; effectiveness of screening/testing: no evidence; effectiveness of supplementation: no evidence or single small trial)
- **(V)L** **(Very)** Low-quality evidence
- **M** Moderate-quality evidence

Population	Outcomes	Association of Serum 25-OHD w/ Outcome*	Effectiveness of Screening/ Testing	Effectiveness of Supplementation (quality of evidence)	Differential Effectiveness of Supplementation (quality of evidence)	Cost-Effectiveness†	OVERALL VALUE OF SCREENING/TESTING (overall quality of evidence)‡
Indications for Which Vitamin D Screening/Testing Could Possibly Have Value							
Healthy§ adults (particularly older adults)	**All-cause mortality Cancer Cardiovascular disease**	✓ (for cancer, positive evidence only for colorectal and ovarian cancer)	**I**	✓**(L)** (mortality) **+/– (L)** (cardiovascular disease) **+/– (L)** (cancer)	✓**(L)** (postmenopausal women; BL serum 25-OHD, but direction of trend varies) **0 (L)** (postmenopausal women; other factors) **I** (adults other than postmenopausal women)	**I**	✓**(VL)** (postmenopausal women) **I** (adults other than postmenopausal women)
Adults w/ osteoporosis or history of fracture	**Musculoskeletal health**	✓	**I**	✓**(M)** (active [pharmaceutical] or high-dose inactive vitamin D) **0 (M)**	**I**	**I**	✓**(M)** (active [pharmaceutical] or high-dose inactive vitamin D) **0 (M)**

Population	Outcomes	Association of Serum 25-OHD w/ Outcome*	Effectiveness of Screening/ Testing	Effectiveness of Supplementation (quality of evidence)	Differential Effectiveness of Supplementation (quality of evidence)	Cost-Effectiveness†	OVERALL VALUE OF SCREENING/TESTING (overall quality of evidence)‡
				(standard dose inactive vitamin D)			(standard dose inactive vitamin D)
Indications for Which Evidence Suggests Vitamin D Screening Likely Has No Value							
Older healthy‡ adults	**Musculoskeletal health**	✓ (BMD) **0** (falls, fractures)	**I**	✓**(L)** (BMD, falls, fractures)	✓**(L)** (conflicting, possibly contradictory findings regarding falls and fractures) **0 (L)** (fractures, BL serum 25-OHD) **0 (L)** (other factors)	Routine supplementation *without screening* is cost-effective in postmenopausal or institutionalized women for preventing fractures.	**0 (L)**
Healthy adults, particularly older adults	**Type 2 diabetes**	✓	**I**	**0 (L)**	**0 (L)** (postmenopausal women; BL serum 25-OHD and other factors) **I** (other adults)	**I**	**0 (L)**
Adults w/ abnormal blood glucose (type 2 diabetes, impaired glucose tolerance, insulin resistance)	**Diabetes-related outcomes**	✓	**I**	✓**(M)**	**0 (L)** (BL serum 25-OHD) **I** (other factors)	**I**	**0 (L)**
Indications for Which the Evidence Is Insufficient to Allow Conclusions About the Value of Vitamin D Screening							
Healthy adults	**Obesity**	**I**	**I**	**+/– (L)**	**0 (L)** (postmenopausal women; numerous factors) **I** (postmenopausal	**I**	**I**

Population	Outcomes	Association of Serum 25-OHD w/ Outcome*	Effectiveness of Screening/ Testing	Effectiveness of Supplementation (quality of evidence)	Differential Effectiveness of Supplementation (quality of evidence)	Cost-Effectiveness†	OVERALL VALUE OF SCREENING/TESTING (overall quality of evidence)‡
					women; BL serum 25-OHD) I (other adults)		
	Depression or other mood disorder	I	I	0(M)	I	I	I
	MS	I	I	I	I	I	I
Healthy adults younger than middle age	Any outcome	I	I	I	I	I	I
Pregnancy	Birth size	I	I	+/– (L)	I	I	I
Lactating women	Any outcome	I	I	I	I	I	I
Adults with obesity	Weight control; cardiometabolic outcomes	I	I	0 (M)	I	I	I
Adults w/ CVD	Blood pressure, CVD events	✓	I	✓(M)	I	I	I
Adults with cancer	Cancer-related outcomes	✓ (individuals with colon cancer, prostate cancer, or melanoma)	I	+/– (L) (outcomes related to advanced prostate cancer) I (outcomes related to other cancer)	I	I	I
Adults with MS	MS-related outcomes	I	I	+/– (L)	I	I	I
Adults with depression	Symptoms, function, QOL	I	I	I	I	I	I
Healthy infants/children/adolescents	Musculoskeletal health	✓	I	+/– (L) (BMC, BMD)	+/– (L) (BL serum 25-OHD) 0 (L) (age) I (other factors)	I	I
	Nonskeletal	I	I	I	I	I	I

Population	Outcomes	Association of Serum 25-OHD w/ Outcome*	Effectiveness of Screening/ Testing	Effectiveness of Supplementation (quality of evidence)	Differential Effectiveness of Supplementation (quality of evidence)	Cost-Effectiveness†	OVERALL VALUE OF SCREENING/TESTING (overall quality of evidence)‡
	outcomes						
Infants/children/adolescents w/ disease	Disease-related outcomes	I	I	I	I	I	I
Any population w/ disease	All-cause mortality	I	I	I	I	I	I

*No definitive cutoff points have been established for any outcomes, but a consensus-based cutoff value of 50 nmol/L has been defined by the Institute of Medicine for optimal bone health in all populations.

†The cost of screening or testing is likely to exceed to the cost of supplementation.

‡Although not reflected elsewhere in the table, safety is taken into account in determining the overall value of screening/testing.

§*Healthy*, as used here, refers to absence of a disease known to cause vitamin D insufficiency, such as chronic kidney disease (CKD), and absence of the types of chronic disease for which vitamin D has been thought to create a risk. Study populations that were unselected on the basis of disease were considered healthy populations.

Key Gaps in the Evidence

The most important gap in the available evidence is that there are no trials designed to assess the direct effect of vitamin D testing on health outcomes, patient behavior, or clinical decision making. There are also substantial gaps in the evidence pertaining to the association between serum levels and outcomes and pertaining to the effectiveness of supplementation, as well as the differential effectiveness of supplementation according to baseline serum levels.

In general, epidemiological studies assessing the association between serum 25-OHD and risk of disease or disease-related outcomes have been somewhat more positive than randomized trials assessing the effect of vitamin D supplementation. Although prospective, longitudinal cohort studies have sometimes shown an association even after adjusting for potential confounders, I confounders may be associated with both good vitamin D status and good health outcomes. Furthermore, as some authors have pointed out, low vitamin D status may be due to unidentified, nonspecific illness that, in turn, is associated with poor health outcomes. Another limitation in many epidemiological studies has been their reliance on a single baseline assessment of serum 25-OHD, which may not always represent vitamin D status over time (Pittas et al., 2010).

If accumulating epidemiological evidence leads to a more evidence-based refinement in the current IOM consensus on optimal serum levels of vitamin D for bone health, or allows determination of different thresholds for different health outcomes, the clinical validity of vitamin D testing (Key Question #1) could improve. A disproportionate amount of evidence related to Key Question #2a, especially for nonskeletal outcomes, came from analyses of a single large trial in which vitamin D was prescribed at half the current IOM recommendation for the age group involved, participants were all postmenopausal women, and baseline vitamin D status was atypically low even for the age group. Thus, future studies may change the overall direction of study results or result in statistically significant pooled estimates of the effectiveness of supplementation where evidence to date has been generally positive but nonsignificant. (On the other hand, a differential effect by vitamin D dose or baseline serum level has not been consistently demonstrated.) Many gaps remain with respect to younger populations, pregnant and lactating women, and subgroups defined by ethnicity and race. Most importantly, more evidence relevant to currently recommended doses of vitamin D and relevant to a wider range of populations and subpopulations might also provide new evidence concerning the differential effect by baseline serum levels, which could have new implications about the utility of testing.

Another gap in the evidence has to do with treatment of osteoporosis. Evidence to date suggests that active vitamin D, but not inactive vitamin D, is effective for reducing bone loss and fractures. However, although megadoses, e.g., 50,000 IU/week, of active vitamin D have been used in healthy populations, no trials were identified that evaluated the use of such doses in individuals who already have evidence of osteoporosis.

Other Considerations

The reviewed practice guidelines, public policy statements, and payer policies do not support routine vitamin D screening. Some recommendations and policies support testing in individuals at high risk of low vitamin D status, but the policies do not always differentiate between conditions that are known to cause vitamin D depletion and general risk factors that have not been established as patient selection criteria for testing or supplementation.

In populations who are likely to have low vitamin D status, screening or testing may be helpful in promoting adherence to prescribed supplementation. Although the analyses of studies conducted in populations of older adults have shown no differential effect according to adherence (where reported, adherence was generally good), there is some evidence of a differential effect by adherence among children. However, there is no evidence that testing, per se, encourages adherence.

LIMITATIONS OF THIS REPORT

The following limitations apply to the methodology used for this report:

- Evidence pertaining to the association between serum levels of vitamin D and health outcomes (clinical validity) was not selected on the basis of an exhaustive search and was not critically appraised. A better depiction of associations, especially with specific nonskeletal outcomes, may have been possible with a more thorough literature search and analysis. However, the review provided in this report does establish that there is a general link between vitamin D and health. The effectiveness of supplementation, especially according to baseline serum levels, speaks more directly to the clinical utility of vitamin D screening and testing.

- This report does not address all of the disease and symptom categories that have been investigated for a link with vitamin D. Specifically, the following areas were omitted:

    - Allergy or autoimmune disease other than multiple sclerosis (MS)
    - Infectious disease
    - Neurological disease
    - Chronic pain

    A cursory review of systematic reviews and randomized controlled trials (RCTs) pertaining to these indications suggests that the quantity of evidence is small and often conflicting. Furthermore, in Washington agency utilization data reviewed during the planning of this report, the diagnoses related to these categories were not as common as the diagnoses in the areas specified in the PICO statement.

- Data from observational studies on the effectiveness of supplementation were not included.

REFERENCES

Aetna. Calcitriol and Paricalcitol Injections. Clinical Policy Bulletin No. 0022. Reviewed March 16, 2012. Available at: http://www.aetna.com/cpb/medical/data/1_99/0022.html. Accessed August 3, 2012.

AGREE Enterprise. Appraisal of Guidelines for Research and Evaluation (AGREE) II. 2012. Available at: http://www.agreetrust.org. Accessed August 3, 2012.

Aloia JF. Clinical Review: The 2011 report on dietary reference intake for vitamin D: where do we go from here*? J Clin Endocrinol Metab*. 2011;96(10):2987-2996.

American Congress of Obstetricians and Gynecologists (ACOG). Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists. Number 117. Gynecologic Care for Women with Human Immunodeficienty Virus. December 2010. Available at: http://www.acog.org/~/media/Practice%20Bulletins/Committee%20on%20Practice%20Bulletins%20--%20Gynecology/Public/pb117.pdf?dmc=1&ts=20120222T2116297804. Accessed August 3, 2012.

American Congress of Obstetricians and Gynecologists (ACOG). Committee on Gynecologic Practice. Committee Opinion. Number 495. Vitamin Dus: Screening and Supplementation During Pregnancy. July 2011. Available at: http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Vitamin_D_-_Screening_and_Supplementation_During_Pregnancy. Accessed August 3, 2012.

American Medical Directors Association (AMDA). *Osteoporosis and fracture prevention in the long-term care setting*. 2009. Summary on National Guideline Clearinghouse [website]. Available at: http://guidelines.gov/content.aspx?f=rss&id=15592. Accessed August 3. 2012.

Bachrach LK, Sills IN. Bone Densitometry in Children and Adolescents. *Pediatrics*. 2011;127(1):189-194.

Bailey BA, Manning T, Peiris AN. Vitamin D testing patterns among six Veterans Medical Centers in the southeastern United States: links with medical costs. *Mil Med*. 2012;177(1):70-76.

Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev*. 2012;2:CD005205.

Bell DS. Protean manifestations of vitamin D deficiency, part 3: association with cardiovascular disease and disorders of the central and peripheral nervous systems. *South Med J.* 2011;104(5):340-344.

Bertone-Johnson ER. Vitamin D and the occurrence of depression: causal association or circumstantial evidence? *Nutr Rev*. 2009;67(8):481-492.

Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. *N Engl J Med*. 2012;367(1):40-49.

Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*. 2011;(7):CD007470.Brooke OG, Brown IR, Bone CD, et al. Vitamin D

supplements in pregnant Asian women: effects on calcium status and fetal growth. *Br Med J*. 1980;280(6216):751-754.

Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. *Nutr Cancer*. 2011;63(6):827-841.

Burton JM, Kimball S, Vieth R, et al. A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. *Neurology*. 2010;74(23):1852-1859.

Buttigliero C, Monagheddu C, Petroni P, et al. Prognostic role of vitamin d status and efficacy of vitamin D supplementation in cancer patients: a systematic review. *Oncologist*. 2011;16(9):1215-1227.

Caan B, Neuhouser M, Aragaki A, et al. Calcium plus vitamin D supplementation and the risk of postmenopausal weight gain. *Arch Intern Med*. 2007;167(9):893-902.

Cannell JJ, Hollis BW. Use of vitamin D in clinical practice. *Altern Med Rev*. 2008;13(1):6-20.

Carter GD. Accuracy of 25-hydroxyvitamin D assays: confronting the issues. *Curr Drug Targets*. 2011;12(1):19-28.

Centers for Medicare & Medicaid Services (CMS). Medicare Coverage Database. Advanced Search: National and Local Coverage Documents [search: *vitamin d*]. Updated August 3, 2012. Available at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Accessed August 3, 2012.

Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *N Engl J Med*. 1992;327(23):1637-1642.

Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. *J Natl Cancer Inst*. 2008;100(22):1581-1591.

Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess (Full Rep)*. 2009;(183):1-420.

Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2011;155(12):827-838.

Clive DR, Sudhaker D, Giacherio D, et al. Analytical and clinical validation of a radioimmunoassay for the measurement of 1,25 dihydroxy vitamin D. *Clin Biochem*. 2002;35(7):517-521.

Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. *Evid Rep Technol Assess (Full Rep)*. 2007;(158):1-235.

Daly RM, Nowson CA. Long-term effect of calcium-vitamin D(3) fortified milk on blood pressure and serum lipid concentrations in healthy older men. *Eur J Clin Nutr*. 2009;63(8):993-1000.

de Boer IH, Tinker LF, Connelly S, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. *Diabetes Care*. 2008;31(4):701-707.

Diaz VA, Mainous AG 3rd, Carek PJ, Wessell AM, Everett CJ. The association of vitamin D deficiency and insufficiency with diabetic nephropathy: implications for health disparities. *J Am Board Fam Med*. 2009;22(5):521-527.

Dumville JC, Miles JN, Porthouse J, Cockayne S, Saxon L, King C. Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *J Nutr Health Aging*. 2006;10(2):151-153.

Edmond K, Bahl R. Optimal feeding of low-birth-weight infants. World Health Organization Technical Review. 2006. Available at: http://www.who.int/maternal_child_adolescent/documents/9241595094/en. Accessed August 21, 2012.

Eftekhari MH, Akbarzadeh M, Dabbaghmanesh MH, Hasanzadeh J. Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients. *Asia Pac J Clin Nutr*. 2011;20(4):521-526.

Endocrine Society. Evaluation, Treatment, and Prevention of Vitamin D Deviciency: An Endocrine Society Clinical Practice Guideline. July 2011. Available at: http://www.endo-society.org/guidelines/final/upload/FINAL-Standalone-Vitamin-D-Guideline.pdf. Accessed August 3, 2012.

Ferguson JH, Chang AB. Vitamin D supplementation for cystic fibrosis. *Cochrane Database Syst Rev*. 2012;4:CD007298.

Frick KD, Kung JY, Parrish JM, Narrett MJ. Evaluating the cost-effectiveness of fall prevention programs that reduce fall-related hip fractures in older adults. *J Am Geriatr Soc*. 2010;58(1):136-141.

Gajic-Veljanoski O, Bayoumi AM, Tomlinson G, Khan K, Cheung AM. Vitamin K supplementation for the primary prevention of osteoporotic fractures: is it cost-effective and is future research warranted? *Osteoporos Int*. 2012. Epub ahead of print. March 6, 2012. Available at: http://www.springerlink.com/content/h0134l27346502q4/?MUD=MP. Accessed August 3, 2012.

George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabet Med*. 2012;29(8):e142-e150.

Gilbert R, Martin RM, Beynon R, et al. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. *Cancer Causes Control*. 2011;22(3):319-340.

Gloth FM 3rd, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging*. 1999;3(1):5-7.

Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. *J Photochem Photobiol B*. 2010;101(2):130-136.

Grimnes G, Figenschau Y, Almås B, Jorde R. Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. *Diabetes*. 2011;60(11):2748-2757.

GroupHealth. Clinical Review Criteria. 2012. Available at: https://provider.ghc.org/open/referralsAndClinicalReview/criteria/index.jhtml?letter=/common/clinical/criteria/index-u.jhtml. Accessed August 3, 2012.

Hadji P, Aapro MS, Body JJ, et al. Management of aromatase inhibitor-associated bone loss in postmenopausal women with breast cancer: practical guidance for prevention and treatment. *Ann Oncol*. 2011;22(12):2546-2555.

Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. *CMAJ*. 2010;182(12):E610-E618.

Harris S, Dawson-Hughes B. Seasonal mood changes in 250 normal women. *Psychiatry Res*. 1993;49(1):77-87.

Hayes, Inc. Hayes Medical Technology Directory. *Vitamin D Supplementation for Patients with Osteoporosis.* Lansdale, PA: Hayes, Inc. August, 2012.

Health Canada. A Consumer's Guide to the DRIs (Dietary Reference Intakes). Modified November 29, 2010. Available at: http://www.hc-sc.gc.ca/fn-an/nutrition/reference/cons_info-guide_cons-eng.php. Accessed August 3, 2012.

Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation*. 2007;115(7):846-854.

Hyppönen E. Vitamin D and increasing incidence of type 1 diabetes-evidence for an association? *Diabetes Obes Metab*. 2010;12(9):737-743.

Institute of Clinical Systems Improvement (ICSI). Routine Prenatal Care. July 2010. Available at: http://www.icsi.org/prenatal_care_4/prenatal_care__routine__full_version__2.html. Accessed August 3, 2012.

Institute of Clinical Systems Improvement (ICSI). Diagnosis and Treatment of Osteoporosis. July 2011a. Available at: http://www.icsi.org/osteoporosis/diagnosis_and_treatment_of_osteoporosis__3.html. Accessed August 3, 2012.

Institute of Clinical Systems Improvement (ICSI). Prevention and Management of Obesity (Mature Adolescents and Adults). April 2011b. Available at: http://www.icsi.org/obesity/obesity_3398.html. Accessed August 3, 2012.

Institute of Clinical Systems Improvement (ICSI). Preventive Services for Children and Adolescents. September 2011c. Available at: http://www.icsi.org/preventive_services_for_children__guideline_/preventive_services_for_children_and_adolescents_2531.html. Accessed August 3, 2012.

Institute of Medicine (IOM). Dietary Reference Intakes for Calcium and Vitamin D. Report Brief. Revised March 2011. Available at: http://www.iom.edu/~/media/Files/Report%20Files/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D/Vitamin%20D%20and%20Calcium%202010%20Report%20Brief.pdf. Accessed August 3, 2012.

Irlam JH, Visser MM, Rollins NN, Siegfried N. Micronutrient supplementation in children and adults with HIV infection. *Cochrane Database Syst Rev*. 2010;(12):CD003650.

Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.

Jacobs ET, Thomson CA, Flatt SW, et al. Vitamin D and breast cancer recurrence in the Women's Healthy Eating and Living (WHEL) Study. *Am J Clin Nutr*. 2011;93(1):108-117.

Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med*. 2008;264(6):599-609.

Jorde R, Sneve M, Torjesen P, Figenschau Y. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. *J Intern Med*. 2010;267(5):462-472.

Kakulavarum N, Moore J. Should Vitamin D Screening be a Part of Primary Care? *Kansas J Med*. 2011:78-83. Available at: http://archie.kumc.edu/bitstream/handle/2271/979/Should%20Vitamin%20D%20Screening%20be%20a%20Part%20of%20Primary%20Care.pdf?sequence=1. Accessed August 8, 2012.

Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. *Mayo Clin Proc*. 2010;85(8):752-757; quiz 757-758.

Khajehei M, Abdali K, Parsanezhad ME, Tabatabaee HR. Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome. *Int J Gynaecol Obstet*. 2009;105(2):158-161.

Kimball S, Vieth R, Dosch HM, et al. Cholecalciferol plus calcium suppresses abnormal PBMC reactivity in patients with multiple sclerosis. *J Clin Endocrinol Metab*. 2011;96(9):2826-2834.

Kumar G, Sachdev H, Chellani H, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. *BMJ*. 2011;342:1-8. Available at: http://www.bmj.com/content/342/bmj.d2975?view=long&pmid=21628364. Accessed August 3, 2012.

LaCroix AZ, Kotchen J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. *J Gerontol A Biol Sci Med Sci*. 2009;64(5):559-567.

Lai JK, Lucas RM, Clements MS, Harrison SL, Banks E. Assessing vitamin D status: pitfalls for the unwary. *Mol Nutr Food Res*. 2010;54(8):1062-1071.

Lappe JM, Travers-Gustafson D, Davies KM, Recker RR, Heaney RP. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *Am J Clin Nutr*. 2007;85(6):1586-1591.Lilliu H, Pamphile R, Chapuy MC, Schulten J, Arlot M, Meunier PJ. Calcium-vitamin D3 supplementation is cost-effective in hip fractures prevention. *Maturitas*. 2003;44(4):299-305.

Looker AC, Johnson CL, Lacher DA, Pfeiffer CM, Schleicher RL, Sempos C. Vitamin D Status: United States, 2001-2006. Hyattsville, MD: National Center for Health Statistics; 2011. NCHS Data Brief No. 59. Centers for Disease Control and Prevention [website]. Available at: http://www.cdc.gov/nchs/data/databriefs/db59.pdf. Accessed August 3, 2012.

Mahon BD, Gordon SA, Cruz J, Cosman F, Cantorna MT. Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J Neuroimmunol*. 2003;134(1-2):128-132.

Major GC, Alarie F, Doré J, Phouttama S, Tremblay A. Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. *Am J Clin Nutr*. 2007;85(1):54-59.

Major GC, Alarie FP, Doré J, Tremblay A. Calcium plus vitamin D supplementation and fat mass loss in female very low-calcium consumers: potential link with a calcium-specific appetite control. *Br J Nutr*. 2009;101(5):659-663.

Mallet E, Gügi B, Brunelle P, Hénocq A, Basuyau JP, Lemeur H. Vitamin D supplementation in pregnancy: a controlled trial of two methods. *Obstet Gynecol*. 1986;68(3):300-304.

Margolis KL, Ray RM, Van Horn L, et al. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. *Hypertension*. 2008;52(5):847-855.

Marques CD, Dantas AT, Fragoso TS, Duarte AL. The importance of vitamin D levels in autoimmune diseases. *Rev Bras Reumatol*. 2010;50(1):67-80.

Marya RK, Rathee S, Dua V, Sangwan K. Effect of vitamin D supplementation during pregnancy on foetal growth. *Indian J Med Res*. 1988;88:488-492.

Maxwell JD, Ang L, Brooke OG, Brown IR. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. *Br J Obstet Gynaecol*. 1981;88(10):987-991.

Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the Perioperative Nutritional, Metabolic, and Nonsurgical Support of the Bariatric Surgery Patient. 2008. Available at: https://www.aace.com/publications/guidelines. Accessed August 8, 2012.

Medical Advisory Secretariat (MAS). Clinical Utility of Vitamin D Testing: An Evidence-Based Analysis. February 2010. Ont Health Technol Assess Ser [website]. Available at: http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_vitamin d_201002.pdf. Accessed August 3, 2012.

Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2010;153(12):815-825.

Mitri J, Dawson-Hughes B, Hu FB, Pittas AG. Effects of vitamin D and calcium supplementation on pancreatic β cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. *Am J Clin Nutr*. 2011b;94(2):486-494.

Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *Eur J Clin Nutr*. 2011a;65(9):1005-1015.

Mosayebi G, Ghazavi A, Ghasami K, Jand Y, Kokhaei P. Therapeutic effect of vitamin D3 in multiple sclerosis patients. *Immunol Invest*. 2011;40(6):627-639.

Mozaffari-Khosravi H, Hosseinzadeh-Shamsi-Anar M, Salami M-A, Hadinedoushan H, Mozayan MR. Effects of a single post-partum injection of a high dose of vitamin D on glucose tolerance and insulin resistance in mothers with first-time gestational diabetes mellitus. *Diabet Med*. 2012;29(1):36-42.

Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. *J Clin Endocrinol Metab*. 2012;97(6):1871-1880.

Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2011;96(10):2997-3006.

Murphy PK, Wagner CL. Vitamin D and mood disorders among women: an integrative review. *J Midwifery Womens Health*. 2008;53(5):440-446.

National Center for Health Statistics (NCHC). Revised Analytical Note for NHANES 2000-2006 and NHANES III (1988-1994) 25-Hydroxyvitamin D Analysis. Revised November 2010. Centers for Disease Control and Prevention [website]. Available at: http://www.cdc.gov/nchs/data/nhanes/nhanes3/VitaminD_analyticnote.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Falls: The assessment and prevention of falls in older people*. Developed by the National Collaborating Centre for Nursing and Supportive Care. London, UK: National Institute for Health and Clinical Excellence; 2004. NICE Clinical Guideline No. 21. Available at: http://www.nice.org.uk/nicemedia/live/10956/29583/29583.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy*. London, UK: National Institute for Health and Clinical Excellence; 2007. NICE Technology Appraisal Guidance No. 117. Available at: http://www.nice.org.uk/nicemedia/live/11608/33857/33857.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Chronic kidney disease: Early identification and management of chronic kidney disease in adults in primary and secondary care*. Developed by the National Collaborating Centre for Chronic Conditions. London, UK: National Institute for Health and

Clinical Excellence; 2008. NICE Clinical Guideline No. 73. Available at: http://www.nice.org.uk/nicemedia/live/12069/42117/42117.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Antenatal care: Routine care for the healthy pregnant woman*. Developed by the National Collaborating Centre for Women's and Children's Health. London, UK: National Institute for Health and Clinical Excellence; 2010. NICE Quick Reference Guide No. 62. Available at: http://www.nice.org.uk/nicemedia/live/11947/40110/40110.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Maternal and child nutrition*. London, UK: National Institute for Health and Clinical Excellence; 2011a. NICE Public Health Guidance Quick Reference Guide No. 11. Available at: http://www.nice.org.uk/nicemedia/live/11943/40092/40092.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women (amended)*. London, UK: National Institute for Health and Clinical Excellence; 2011b. NICE Technology Appraisal Guidance No. 190. Available at: http://www.nice.org.uk/nicemedia/live/11746/47176/47176.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (amended)*. London, UK: National Institute for Health and Clinical Excellence; 2011c. NICE Technology Appraisal Guidance No. 161. Available at: http://www.nice.org.uk/nicemedia/live/11748/42447/42447.pdf. Accessed August 8, 2012.

National Institute for Health and Clinical Excellence (NICE). *The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care*. London, UK: National Institute for Health and Clinical Excellence; 2012. NICE Clinical Guideline No. 137. Available at: http://www.nice.org.uk/nicemedia/live/13635/57779/57779.pdf. Accessed August 8, 2012.

Nikooyeh B, Neyestani TR, Farvid M, et al. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. *Am J Clin Nutr*. 2011;93(4):764-771.

Nilas L, Christiansen C. Treatment with vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. *Int J Obes*. 1984;8(5):407-411.

Ortega RM, López-Sobaler AM, Aparicio A, et al. Vitamin D status modification by two slightly hypocaloric diets in young overweight/obese women. *Int J Vitam Nutr Res*. 2009;79(2):71-78.

Parker G, Brotchie H. "D" for depression: any role for vitamin D? "Food for Thought" II. *Acta Psychiatr Scand*. 2011;124(4):243-249.

Pelajo CF, Lopez-Benitez JM, Miller LC. Vitamin D and autoimmune rheumatologic disorders. *Autoimmun Rev*. 2010;9(7):507-510.

Pierrot-Deseilligny C. Clinical implications of a possible role of vitamin D in multiple sclerosis. *J Neurol*. 2009;256(9):1468-1479.

Pittas AG, Chung M, Trikalinos T, et al. Systematic review: vitamin D and cardiometabolic outcomes. *Ann Intern Med*. 2010;152(5):307-314.

Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: A systematic review and meta-analysis. *Eur J Intern Med*. 2012;23(5):465-469.

Regence Group. Laboratory Section - Vitamin D Testing. Medical Policy No. 52. Effective November 1, 2011. Available at: http://blue.regence.com/trgmedpol/lab/lab52.html. Accessed August 3, 2012.

Rosenblum JL, Castro VM, Moore CE, Kaplan LM. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. *Am J Clin Nutr*. 2012;95(1):101-108.

Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. *Br J Psychiatry*. 2011;198(5):357-364.

Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2006;83(4):754-759.

Schnatz PF. The 2010 North American Menopause Society position statement: Updates on screening, prevention and management of postmenopausal osteoporosis. *Conn Med*. 2011;75(8):485-487.

Seeley D, Kanji S, Yazdi F, et al. Dietary Supplements in Adults Taking Cardiovascular Drugs. Comparative Effectiveness Review Number 51. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. HHSA 290-2007-10059-I.) AHRQ Publication No. 12-EHC021-EF. Rockville, MD: Agency for Healthcare Research and Quality. April 2012. Available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1038. Accessed August 11, 2012.

Singh S, Sun H, Anis AH. Cost-effectiveness of hip protectors in the prevention of osteoporosis related hip fractures in elderly nursing home residents. *J Rheumatol*. 2004;31(8):1607-1613.

Sneve M, Figenschau Y, Jorde R. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects. *Eur J Endocrinol*. 2008;159(6):675-684.

Soilu-Hänninen M, Aivo J, Lindström B-M, et al. A randomised, double blind, placebo controlled trial with vitamin D3 as an add on treatment to interferon β-1b in patients with multiple sclerosis. *J Neurol Neurosurg Psychiatr*. 2012;83(5):565-571.

Straube S, Derry S, Moore RA, McQuay HJ. Vitamin D for the treatment of chronic painful conditions in adults. *Cochrane Database Syst Rev*. 2010;(1):CD007771.

Tang JY, Fu T, Leblanc E, et al. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. *J Clin Oncol*. 2011;29(22):3078-3084.

Thomas GN, Scragg R, Jiang CQ, et al. Hyperglycaemia and vitamin D: a systematic overview. *Curr Diabetes Rev*. 2012;8(1):18-31.

Touvier M, Chan DS, Lau R, et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev*. 2011;20(5):1003-1016.

Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ*. 2003;326(7387):469.

U.S. Preventive Services Task Force (USPSTF). Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease. June 2003. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspsvita.htm. Accessed August 8, 2012.

U.S. Preventive Services Task Force (USPSTF). Prevention of Falls in Community-Dwelling Older Adults. Recommendation Statement. May 2012a. Available at: http://www.uspreventiveservicestaskforce.org/uspstf11/fallsprevention/fallsprevrs.htm. Accessed August 8, 2012.

U.S. Preventive Services Task Force (USPSTF). Vitamin D and Calcium Supplementation to Prevent Cancer and Osteoporotic Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement (DRAFT). Summary of Recommendations and Evidence. July 2012b. Available at: http://www.uspreventiveservicestaskforce.org/uspstf12/vitamind/draftrecvitd.htm. Accessed October 3, 2012.

Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354(7):684-696.

Wagner CL, Greer FR. Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents. *Pediatrics*. 2008;122(5):1142-1152.

Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. *Breastfeed Med*. 2006;1(2):59-70.

Wang S. Epidemiology of vitamin D in health and disease. *Nutr Res Rev*. 2009;22(2):188-203.

Winzenberg T, Powell S, Shaw KA, Jones G. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. *BMJ*. 2011;342:c7254.
Witham MD, Crighton LJ, Gillespie ND, Struthers AD, McMurdo ME. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure: a randomized controlled trial. *Circ Heart Fail*. 2010;3(2):195-201.

Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. *J Hypertens*. 2009;27(10):1948-1954.

World Health Organization (WHO). Vitamin and mineral requirements in human nutrition. Second edition. 2004. Available at: http://www.who.int/nutrition/publications/micronutrients/9241546123/en. Accessed August 18, 2012.

World Health Organization (WHO). WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia. 2011. Available at: http://www.who.int/maternal_child_adolescent/documents/preeclampsia_eclampsia/en. Accessed August 18, 2012.

Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: circulating vitamin D and ovarian cancer risk. *Gynecol Oncol*. 2011a;121(2):369-375.

Yin L, Grandi N, Raum E, Haug U, Arndt V, Brenner H. Meta-analysis: serum vitamin D and colorectal adenoma risk. *Prev Med*. 2011b;53(1-2):10-16.

Yuan C, Kosewick J, He X, Kozak M, Wang S. Sensitive measurement of serum 1α,25-dihydroxyvitamin D by liquid chromatography/tandem mass spectrometry after removing interference with immunoaffinity extraction. *Rapid Commun Mass Spectrom*. 2011;25(9):1241-1249.

Zhang HL, Wu J. Role of vitamin D in immune responses and autoimmune diseases, with emphasis on its role in multiple sclerosis. *Neurosci Bull*. 2010;26(6):445-454.

Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. *Am J Clin Nutr*. 2009;89(5):1321-1327.

Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. *Am J Clin Nutr*. 2012;95(1):91-100.

APPENDICES

APPENDIX I. Search Strategy

Database

MEDLINE

Search for Systematic Reviews and Practice Guidelines (March 2012)

Initially, evidence for this report was obtained by searching for relevant systematic reviews and guidelines in the following databases: Blue Cross Blue Shield TEC Assessments, Canadian Agency for Drugs and Technology in Health (CADTH), Centre for Reviews and Dissemination (York University), Cochrane Library, the National Institute for Health and Clinical Excellence (NICE), and the Trip Database (which links to the National Guidelines Clearinghouse of the Agency for Healthcare Research and Quality [AHRQ]). Additional systematic reviews were selected from a search of the MEDLINE database (PubMed) using *vitamin D* as a keyword and applying these limits:

- Limited to Practice Types: meta-analysis, practice guideline, consensus development conference, NIH*
- Limited to Journal Groups: systematic review*
- Last 10 years

*Two separate searches, connected by "OR"

These searches identified the AHRQ report on vitamin D and calcium and health outcomes (Chung et al., 2009), which then served as a source of evidence pertaining to outcomes in healthy populations and guided additional searches.

PubMed Search Strategy for Randomized Controlled Trials (RCTs) (April 30, 2012; update July 31, 2012)

The following strategy was used to identify all of the relevant RCTs in healthy populations published in 2009 or later, to overlap with the end of the search (April 2009) conducted by Chung et al. (2009) for the AHRQ report on vitamin D and calcium and health outcomes. This search also served to identify recent RCTs conducted in disease populations since all of the selected systematic reviews were based on searches ending in 2009 or later.

#8 Search (#7) AND #6 Limits: Humans, Publication Date from 2009/01/01 to 2012
#7 Search (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) Limits: Humans, Publication Date from 2009/01/01 to 2012
#6 Search ((((#5) OR #4) OR #3) OR #2) OR #1
#5 Search "Vitamin D Deficiency/diet therapy"[Mesh] OR "Vitamin D Deficiency/therapy"]

#4 Search "Ergocalciferols/administration and dosage"[Mesh] OR "Ergocalciferols/therapeutic use"[Mesh]
#3 Search "Cholecalciferol/administration and dosage"[Mesh] OR "Cholecalciferol/therapeutic use"[Mesh]
#2 Search ("Vitamin D/administration and dosage"[Mesh] OR "Vitamin D/therapeutic use"[Mesh])
#1 Search (supplement or supplementation or diet) and (vitamin D)

The foregoing search was combined with relevant keywords and Mesh terms to identify RCTs published in 2008 or earlier for the disease populations that were not addressed in systematic reviews (obesity, cardiovascular disease other than hypertension, depression, and mood disorders). In addition, searches were conducted to make sure that pre-April 2009 relevant studies in pregnant women (*pregnant* or *pregnancy* as a keyword), low-birthweight infants, and nonadult populations (Child: 0-18 years limit) had not been missed by the AHRQ report by Chung et al. (2009).

Searches for Cost Studies or Economic Evaluations

The National Health Service Economic Evaluation Database (NHSEED) was searched with the keyword vitamin D. In addition, MEDLINE was searched using this search string, combined with *vitamin D*:

((((economic analysis) OR (economic evaluation)))) OR (((((cost AND (analysis OR benefit OR effective* OR consequence OR minimization)))) OR (("Costs and Cost Analysis"[MeSH] OR "Cost-Benefit Analysis"[MeSH]))))

Additional Searches for Practice Guidelines

In addition to the sources searched for systematic reviews, websites for the American College of Obstetricians and Gynecologists (ACOG), American Academy of Family Physicians (AAFP), and American College of Physicians (ACP) were searched.

APPENDIX II. Overview of Evidence Quality Assessment Methods

Tools used include internally developed Quality Checklists for evaluating the quality (internal validity) of different types of studies, a checklist for judging the adequacy of systematic reviews used instead of de novo analysis, and Hayes Evidence-Grading Guides for evaluating bodies of evidence for different types of technologies. Hayes methodology is in alignment with the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system, which was developed by the GRADE Working Group, an international collaborative body.

Step 1	Individual study appraisal a. Initial rating according to study design *Good:* Randomized Controlled Trials *Fair:* Nonrandomized Trial (controlled, parallel group, quasi-randomized) *Poor:* Observational Analytic Studies (prospective or retrospective trials involving historical controls, pretest posttest control trial [patients legitimately serve as their own controls], case-control, registry/chart/database analysis involving a comparison group) *Very Poor:* Descriptive Uncontrolled Studies (case reports, case series, cross-sectional surveys [individual-level data], correlation studies [group-level data]) b. Consider the methodological rigor of study execution according to items in a proprietary Quality Checklist c. Repeat for each study
Step 2	Evaluation of each body of evidence by outcome, key question, or application a. Initial quality designation according to *best* study design in a body of evidence b. Downgrade/upgrade *Downgrade factors:* Study weaknesses (Quality Checklists), lack of applicability, inconsistency of results, small quantity of data, publication bias (if adequate information is available) *Possible upgrade factors:* Strong association, dose-response effect, bias favoring no effect c. Assign final rating: High-Moderate-Low-Very Low d. Repeat for each outcome/question/application
Step 3	Evaluation of overall evidence a. Rank outcomes by clinical importance b. Consider overall quality of the evidence for each *critical* outcome c. Assign overall rating based on lowest-quality body: High-Moderate-Low-Very Low
Step 4	Evidence-based conclusion Overall quality of the evidence + Balance of benefits and harms

APPENDIX III. Vitamin D Supplementation for Promotion of Musculoskeletal Health: Findings from Systematic Reviews

Key:; 25-OHD, 25-hydroxyvitamin D; AHRQ, Agency for Healthcare Research and Quality; BL, baseline; BMC, bone mineral content; BMD, bone mineral density; CCRCT, Cochrane Central Register of Controlled Trials; CI, confidence interval (95% unless otherwise noted); CLIA, chemiluminescent immunoassay; CONSORT, Consolidated Standards of Reporting Trials; CPBA, competitive protein binding assay; DRI, Dietary Reference Intakes; EAR, estimated average requirement; EPC, Evidence-Based Practice Center; f/u, follow-up; grp(s), group(s); HR, hazard ratio; hx, history; IOM, Institute of Medicine; ITT, intention-to-treat; IU, international units; MA, meta-analysis; NICE, National Institute for Health and Clinical Excellence; nmol, nanomole; NR, not reported; NS, not (statistically) significant; OR, odds ratio; pt(s), patient(s); PTH, parathyroid hormone; RCT, randomized controlled trial; RDA, recommended daily allowances; RIA, radioimmunoassay; RR, relative risk; sig, significant; SMD, standard mean difference; SR, systematic review; tx, treatment; USPSTF, U.S. Preventive Services Task Force; vitD, vitamin D; WMD, weighted mean difference

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
Cranney et al. (2007) (Ottawa EPC) AHRQ report to provide support for evidence-based EAR and RDA values to be determined by the IOM, w/ an emphasis on musculoskeletal outcomes such as **BMC/BMD, physical performance, and falls**. *Databases searched:* MEDLINE, Embase, CINAHL, AMED, Biological Abstracts, CCRCT *Search time frame:* June 2006 *Included RCTs assessing BMC/BMD or falls:* Greer 1982 (infants); Corless 1985; Ala-Houhala 1988 (older children); Ooms 1995; Keane 1998; Storm 1998; de John 1999; Schaafsma 2002; Bishoff-Ferrani 2003; Chee 2003; Cooper 2003;	17 RCTs for effect of supplementation or fortified food (w/ target vitD intake) on BMD; 3 RCTs for effect on or association of change in serum 25-OHD w/ physical performance measures *Populations of interest:* Children and adults *Intervention of interest:* Supplemental vitD2 or vitD3 and calcium; fortified foods (no RCTs of vitD-fortified food) *Musculoskeletal outcomes of interest:* BMC, BMD, fractures, falls, physical performance (only studies/data pertaining to BMC/BMD and physical performance, including falls, are presented here). See Chung et al. (2011) for a more recent assessment of fracture. *Study inclusion criteria:* English language; RCTs and observational studies (only data from RCTs presented	Qualitative review, w/ quantitative analysis of effect on BMD in 11 trials in adult populations. *Study quality assessment:* Jadad scale (1-5; ≥3 = higher quality) + allocation concealment for RCTs. *Overall evidence quality assessment:* Good = consistent, ≥1 study of higher quality; fair = sufficient to determine association but limited by consistency, quantity, or study quality; inconsistent = conflicting results preclude conclusion. VitD deficiency defined as serum 25-OHD <30 nmol/L.	*BMD, quantitative analysis, adults:* VitD3+calcium vs placebo: Small effect on lumbar spine, femoral neck, and total body BMD (WMD range 0.60-1.40, all sig) (7 RCTs). NS for effect on forearm (1 RCT). VitD3+calcium vs calcium: NS in 5 RCTs; small effect on BMD in femoral neck (1 RCT). VitD3 vs placebo: Small effect on BMD in femoral neck (1 RCT); NS but wide CI (WMD=0.06; CI, –3.74 to 3.86), forearm (1 RCT). *BMD/BMC, qualitative findings by population:* Infants: Inconsistent findings (2 RCTs) (quality fair-high). Older children and adolescents: Inconsistent across sites (2 RCTs) (higher quality). Postmenopausal women and older men: No effect in 5 RCTs; positive effect in 1 RCT (quality fair-high).	VitD supplementation at doses ≤800 IU/day, particularly when combined w/ calcium, may have a small effect on BMD/BMC and/or physical performance in older adults, but effects in pediatric and younger adult populations require further study. Preliminary evidence suggests testing for vitD status is not necessary for selection of pts likely to experience improvement in bone health w/ vitD supplementation. *Quality of available evidence according to Cranney et al.:* 13 trials were of higher quality on Jadad scale but did not adequately report allocation concealment.

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
Kenny 2003; Dhesi 2004; Aloia 2005; Johnson 2005; Daly 2006; Fuleihan 2006 (child and adolescent girls) NOTE: Information about and data from selected observational studies, RCTs that did not include a no-tx or placebo grp, and RCTs that did not assess BMD, BMC, or physical performance are not presented here.	here) *Study exclusion criteria:* Vitamin D analogs, secondary osteoporosis, vitD-dependent rickets *Study characteristics:* Pediatric: 3 RCTS; small sample sizes; duration of tx 2-12 mos; vitD doses 400 IU/day except for 200 IU/day or 2000 IU/day in 1 RCT in older/adolescent girls). Adults: 14 RCTs; predominately late menopausal women (1 small RCT included premenopausal women); small sample sizes, 2-3 yrs tx duration; mean BL 25-OHD, 25-97 nmol/L; VitD doses generally ≤800 IU; most RCTs used vitD3+calcium. No RCTs in pregnant/lactating women; no RCTs evaluating rickets as outcome. *Assays used:* Where reported by Cranney et al., generally CPBA; 2 instances of RIA		*Physical performance, including falls:* Inconsistent findings (4 RCTs, quality fair-good). *Effect of pt characteristics:* Where reported (few trials), BL serum 25-OHD was not associated w/ tx effect. In 1 RCT assessing effect on falls (Bischoff-Ferrani 2003), vitD was associated w/ fall reduction after adjustment for both BL 25-OHD and hx of falls. *Authors' conclusions w/ regard to the effect of supplementation on BMD:* VitD3+calcium has a small effect on BMD in women of reproductive age, postmenopausal women, and older men. VitD3 alone may be of less benefit in calcium-replete postmenopausal women.	*Limitations of SR:* No serious limitations, but no analysis by duration of tx.
Chung et al. (2009) AHRQ report to support IOM possible revision of DRI SR and MA to summarize the evidence on the relationship between vitamin D, calcium, and a combination of both w/ a wide range of health outcomes identified by IOM, including **BMC/BMD, physical performance, and falls**. *Databases searched (Chung 2009):* MEDLINE, CCRCT, Cochrane Database of Systematic Reviews, and the Health	1 SR (Cranney 2007) and 9 new RCTs selected for assessment of the effect of vitD or vitD+calcium supplementation on incidence of BMD and falls (Assessment of other outcomes not presented here.) *Population of interest:* General population of otherwise healthy people to whom DRI recommendations are applicable *Interventions of interest:* See Cranney et al. (2007) *Assessed outcomes relevant to musculoskeletal health, other than*	*Study quality assessment grades:* A (results valid w/in the limits of interpretation for that study design); B (susceptible to some bias; C (significant bias that may invalidate results). NOTE: Quality assessments do not reflect strength of basic study design. *Adjustment for confounding:* Most studies adjusted for ≥2 confounders; adequacy of adjustment taken into account in quality rating.	See Cranney et al. (2007) for findings in RCTs published June 2006 or before. *BMD/BMC:* In the newly published RCTs, effects of vitD alone on BMC/BMD (children/adolescents, 3 poor-fair RCTs) or BMD (adults, 4 generally fair-good RCTs) were small (difference in % change, –0.3% to 7.0% and, in most studies, NS, but CIs around differences in % change were large in some studies of postmenopausal women. *Physical performance:* Very small between-group differences in change. Significant for chair stands and walking time; NS for grip strength (1 poor RCT).	New evidence included in the report is consistent w/ the conclusion of Cranney et al. (2007) w/ respect to vitD+calcium in postmenopausal women, i.e., that vitD supplementation has, at best, small positive effects on BMD and physical performance; suggests small effects on BMD in adolescent girls and on stress fractures in healthy Navy recruits; and identifies new populations in which vitD

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
Technology Assessments (English-language only) *Search time frame (Chung 2009):* 1969 – December 2008 for SRs and for outcomes of upper limits; April 2009 for outcomes of EARs *Funding source:* AHRQ NOTE: This review updates and expands on a previous AHRQ report on *Effectiveness and Safety of Vitamin D in Relation to Bone Health* (Cranney et al., 2007). Information about and data from observational studies, and from RCTs assessing fractures and assessing outcomes unrelated to musculoskeletal health, are not presented here.	*fractures:* BMD, physical performance, falls *Study inclusion criteria:* English language; RCTs and observational studies reporting outcomes in relation to vitD and/or calcium; only results of RCTs are reported here *Study exclusion criteria:* Vitamin D analogs; study populations where >20% had chronic disease (older populations excepted) *Characteristics of RCTs published after search by Cranney et al. (2007):* <u>5 new RCTs, BMD</u>: Cheng 2005 (C): n=85 healthy girls (age 10-12 yrs); 62°24'N; BL 25-OHD NR; vitD2 200 IU+calcium vs placebo; f/u 24 mos; 65% completion w/ >50% compliance El-Hajj 2006 (girls) (C): n=168 adolescent girls; 33°53'N; BL 25-OHD 34.9 nmol; weekly oral VitD equivalent to 200 IU/day or 2000 IU/day vs placebo; high compliance Moschonis 2006 (C): n=75 postmenopausal women (mean age 61); 31°N; BL 25-OHD NR; vitD3 300 IU/day+prescribed dose of dietary calcium vs usual diet; f/u 12 mos; high compliance Bolston-Smith 2007 (B): n=106 women ≥60 yrs; 54°N; BL 25-OHD 59.4 nmol/L; vitD3 400 IU/day+calcium vs placebo; f/u 24 mos; good compliance Andersen 2008 (B): n=60 adolescent girls, men (age 18-64 yrs), or women		*Falls:* HR=0.95 (CI, 0.79-1.15; NS) (Lyons 2007); RR=0.82 (CI, 0.59-1.16; NS) (Burleigh 2007); NS difference in fall-free survival curves (Bunout 2006) *Stress fracture:* RR=0.8 (CI, 0.64-0.99; *P*=0.026); OR=0.79 (CI, 0.62-1.01; *P*=0.059) (Lappe 2008) *Other fracture:* See Chung et al. (2011) *Effect of pt characteristics:* Not discussed *Assay kits:* Large variation, according to authors, but specifics not discussed. *Authors' conclusions:* In the Summation section, the conclusion of Cranney et al. (2007) w/ regarding to vitD3+calcium in postmenopausal women was cited; no other conclusions about musculoskeletal health were stated.	supplementation may reduce falls. *Quality of available studies according to Chung et al.:* Potential bias in most studies, especially in older adults; generally fair. *Other comments:* VitD doses were usually less than current IOM recommendations. *Limitations of the SR:* No analysis according to BL pt factors or duration of tx.

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
	(age 18-53 yrs); 55°N; BL 25-OHD 11 nmol/L (adolescent girls), 12 nmol/L (women), 21 nmol/L (men); VitD3 400 IU/day or vitD3 800 IU/day vs placebo; good compliance in adults Zhu 2008a (A): n=256 elderly women; 32°S; BL 25-OHD 44.3 nmol/L; VitD2 1000 IU/day+calcium vs calcium alone; good compliance Zhu 2008b (B): n=69 elderly women (mean age 75 yrs); Western Australia; BL 25-OHD 68.0 nmol/L; vitD2 1000 IU/day+calcium vs placebo; f/u 60 mos; good compliance 2 new RCTs, falls: Burleigh 2007 (C): n= 203 inpatients w/ high comorbidity; 60% women; BL 25-OHD 22.0 nmol/L; vitD3 800 IU/day+calcium vs calcium alone; good compliance; interquartile range for time to fall, 15-71 days Bunout 2006 (C): n=healthy adults (mean age 76 yrs; 88% women); BL 25-OHD ≤40; vitD 400 IU/day+calcium vs calcium alone; high compliance; mean f/u 9 mos 1 new RCT, stress fracture Lappe 2008 (B): n=8901 healthy Navy recruits (mean age 19 yrs; 100% women); 41°N; BL 25-OHD NR; vitD 800IU/day+calcium vs placebo (n=5201) or vitD 400 IU/day+calcium vs placebo (n=3700); mean f/u 2 mos 1 new RCT, physical performance Brunner 2008 (C): n=2347 postmenopausal women; BL 25-OHD NR; vitD 400IU/day+calcium vs placebo			
Michael et al. (2010)	9 RCTs (5780 participants); excludes 2	Random-effects meta-analysis	*Overall RR, vitD w/ or w/o calcium:*	Authors' conclusions are

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
USPSTF Review (funded by AHRQ) SR and MA to describe the benefits and harms of interventions that could be used by primary care practitioners to prevent **falls** among **community-dwelling older adults** *Databases searched:* MEDLINE, CCRCT, Cochrane Database of Systematic Reviews, CINAHL; website of AHRQ, IOM, and NICE *Search time frame:* 1992 – February 2010 *Included RCTs assessing vitD:* Pfeifer 2000, Gallagher 2001, Dhesi 2004, Dukas 2004, Porthouse 2005, Bischoff-Ferrari 2006, Prince 2008, Pfeifer 2009, Kärkkäinen 2010 (plus Sanders 2010 in ad hoc reanalysis) NOTE: Only data and conclusions from RCTs of vitD are presented here.	studies (Bunout 2006, Burleigh 2007) covered by Chung et al. (2009) because these did not take place in community settings *Population/settings of interest:* Community-dwelling adults, avg age ≥65 yrs; settings generalizable to U.S. primary care *Interventions of interest:* Multiple, including vitD or vitD+calcium *Outcomes of interest:* Falls, harms (only falls presented here) *Study inclusion criteria:* English-language RCTs deemed to be of good or fair quality *Study characteristics:* Primarily non-Hispanic white women; 5 trials in high-risk populations (either recent falls or vitD deficiency); median dose vitD, 800 IU/day (range 10-1000 IU/day, except for 1-time injection of 600,000 IU in 1 trial); median duration of tx, 12 mos (range 8 wks – 3 yrs); 2 studies used vitD2, otherwise vitD3; vitD combined w/ calcium in 6 trials; control grps were no intervention, placebo, or calcium alone	since outcome measures varied (# fallers [most frequent], fall rate, time to first fall, # frequent fallers). Random-effects metaregression to examine potential sources of heterogeneity, i.e., effect modifiers: Mean age, population w/ avg age ≥80 yrs, proportion of women, proportion w/ hx of falling in previous yr, comprehensiveness/intensity of intervention, inclusion of high-risk participants (high risk not defined). *Study quality assessment:* USPSTF criteria (comparability of grps, differential loss to f/u or overall high loss to f/u, clear definition of intervention, reliable/valid outcome measurement, ITT analysis	RR=0.83 (CI, 0.77-0.89); NS statistical heterogeneity. RRs in individual studies ranged from 0.60-0.98 and were generally NS (CIs crossed null). Reanalysis, including a trial (Sanders 2010) published after the search ended and showing an increase in falls w/ a 1-time dose of 500,000 IU, yielded a new estimate of RR=0.83 (CI, 0.71-0.979). The other included RCT using a megadose (Dhesi 2004) reported neither a positive or negative effect on risk of falling. *Effect of pt characteristics on pooled estimate:* None according to age, sex distribution, hx of falls, or risk status (hx of falls or vitD deficiency). *Authors' conclusion:* VitD supplementation can reduce falls in community-dwelling older adults.	valid and apply most closely to standard vitD doses (median 800 IU/day). A finding of no effect modification by risk status, including vitD deficiency, suggests that vitD testing in community-dwelling older adults is not necessary to select pts likely to benefit from supplementation. *Quality of available evidence according to Michael et al.:* All vitD studies, fair; most trials underpowered and most assessed self-reported falls retrospectively w/ recall of 6 wks – 12 mos. *Limitations of SR:* No serious limitations; no assessment according to tx duration.
Chung et al. (2011) USPSTF Focused Update Review (funded by AHRQ) Focused update SR-MA to assess the benefits and harms of vitD supplementation w/ or w/o calcium on outcomes of cancer	16 RCTs assessing effect on fractures *Populations of interest:* General population of otherwise healthy people to whom DRI recommendations are applicable *Interventions of interest:* VitD	*Meta-analysis:* Random effects model; 1 fracture outcome from each study according to the following preferences in descending order: total fracture, hip fracture, nonvertebral fracture. Heterogeneity tested according to Cochran Q statistic (significant if	*RR of fracture, vitD w/ or w/o calcium vs placebo in elderly men and women:* Overall: RR=1.03 (CI, 0.84-1.26; moderate heterogeneity) (5 RCTs); RRs in individual studies ranged from 0.80-1.33) Institutionalized: RR=0.99 (CI, 0.72-1.34; low heterogeneity) (2 RCTs)	Results are inconclusive w/ respect to vitD alone. VitD+calcium is modestly effective in reducing fracture in older adults, w/ less certainty concerning men than postmenopausal women.

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
and **fractures** in adults *Databases searched:* MEDLINE, Cochrane Central Register of Controlled Trials (English language only) *Search time frame:* Through July 2011 (as an update to Chung et al. (2009) NOTE: This review serves as a focused update of a previous AHRQ report on *Vitamin D and Calcium: A Systematic Review of Health Outcomes* (Chung et al., 2009). Only interventional evidence pertaining to vitD supplementation and fractures presented here.	supplementation alone or in combination w/ calcium *Outcomes of interest:* Fractures, cancer, adverse events (only assessment of fracture presented here) *Study inclusion criteria:* RCTs comparing vitD alone of vitD+calcium w/ no supplementation or w/ placebo; studies of pregnant women only *Study exclusion criteria:* ≥20% of study participants had major chronic disease, such as diabetes or cardiovascular disease at BL, w/ the exception of elderly (≥65 yrs)participants, who could have chronic disease other than cancer; tx duration <1 mo; synthetic vitD analogs *Study characteristics:* VitD alone: 5 RCTs (n=14,583 elderly men and women; mean age 75-85 yrs; mean BL 25-OHD, 26-59 where reported; vitD 822-1370 IU/day; f/u 7 mos – 5 yrs) (Lips 1996, Law 2006, Lyons 2007, Trivedi 2003, Sanders 2010) VitD+calcium: 11 RTCs (n=52,915; 69% postmenopausal women; mean age 53-85 yrs; mean BL 25-OHD, 15-50, where reported; vitD 300-1100 IU/day, generally 800 IU/day; f/u 1-7 yrs) (Dawson-Hughes 1997; Chapuy 1992, Komulainen 1998, Pfeiffer 2000; Chapuy 2002, Harwood 2004, Flicker 2005, Grant 2005, Porthouse 2005, Jackson 2006, Salovaar 2010)	<0.10) and quantified as I^2 (low, 25%; moderate, 50%; high, 75%) *Metaregression:* To assess whether effects depend on daily dose or BL serum concentration; random effects model *Study quality assessment:* AHRQ methods (see Chung et al., 2009) applied to CONSORT items	Community dwelling: RR=1.06 (CI, 0.77-1.46; high heterogeneity) (3 RCTs) *RR of fracture, vitD+calcium vs placebo in mostly postmenopausal women:* Overall: RR=0.88 (CI, 0.79-0.99; low heterogeneity) (11 RCTs; RRs in individual studies ranged from 0.0.46-1.08) Institutionalized: RR=0.71 (CI, 0.57-0.89; no heterogeneity) (3 RCTs) Community dwelling: RR=0.89 (CI, 0.76-1.04; low heterogeneity) (6 RCTs) Community dwelling w/ hx of fracture: RR=1.02 (CI, 0.89-1.16; no heterogeneity) (2 RCTs) *Meta-regression analysis of RR:* Per 100-IU increase in vitD dose: RR=1.01 (CI, 0.97-1.07) (16 RCTs) Per 100 IU increase in BL serum 25-OHD: RR=1.02 (CI, 0.86-1.2) (12 RCTs) *Authors' conclusions:* VitD+calcium supplementation can reduce fracture risk, but the effects may be smaller among community-dwelling older adults than among institutionalized elderly persons.	*Quality of included evidence, according to Chung et al.:* 5 RCTs of vitD alone were of good (1), fair (3), and poor (1); 11 RCTs of vitD+calcium were good (2), fair (5), and poor (4), according to Chung et al. May not be applicable to adults <50 yrs. *Limitations of the SR:* Results may not be applicable to specific types of fracture or represent a precise estimate of effect on total fracture since only 1 fracture outcome was selected from each study; no analysis of effect according to duration of tx or assay used to measure BL serum levels. *Other comments:* No studies directly compared outcomes in institutionalized and community-dwelling individuals; wide CIs.-o
Murad et al. (2011)	26 RCTs (45,782 participants)	Random-effects MA; I^2 to assess	*Overall OR:* OR=0.86 (CI, 0.77-0.96), range	Authors' conclusions seem

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
(Commissioned and funded by The Endocrine Society) SR-MA to assess the effectiveness of vitD supplementation in preventing **falls** *Databases searched:* MEDLINE, Embase, Web of Science, SCOPUS, PEDRO, regional databases *Search time frame:* Through August 2010 *Included RCTs (studies in institutionalized populations are underscored):* Chapuy 1992, Graffmans 1996, Peichl 1999, Pfeifer 2000, Chapuy 2002, Bischoff 2003, Latham 2003, Trivedi 2003, Dhesi 2004, Harwood 2004, Flicker 2005, Grant 2005, Larsen 2005, Porthouse 2005, Sato 2005, Arden 2006, Bischoff-Ferrari 2006, Law 2006, Broe 2007, Burleigh 2007, Kärkkäinen 2010, Berggren 2008, Prince 2008, Pfeifer 2009, Sanders 2010, Witham 2010) NOTE: 2 RCTs included by Michael et al. (2010) were not included in this review: Gallagher 2001, Dukas 2004. 1 RCT included by Chung et al. (2009) was not included in this review: Bunout 2006	*Population of interest:* Adults *Intervention of interest:* VitD w/ or w/o calcium *Outcome of interest:* # persons who experienced ≥1 fall *Study inclusion criteria:* RCTs w/ a control grp that did not receive the vitD intervention; no language restriction *Study exclusion criteria:* Use of calcitriol or one of its analogs *Study characteristics:* Mean age 76 yrs; 78% women; median risk of falls, 50% (range 15%-69%); median duration of tx, 12 mos (range 3-62); BL 25-OHD levels NR for most trials; vitD3 at 400-1000 IU/day in most studies; D2 or D3 at 100,000-600,000 IU once, twice, at 4 mos, or annually in 7 studies, usually combined w/ calcium; adherence ≥80% or NR; most pts vitD deficient	statistical heterogeneity (≤25% = low, 50% = moderate, ≥75% = high); publication bias assessed by visual inspection of funnel plot and Egger's regression test. Subgrps defined a priori for assessment of inconsistency and tx interactions. VitD deficiency determined independently by 2 reviewers according to 1 of 3 criteria: author description, BL 25-OHD, or enrollment of pts w/ ≥2 deficiency risk factors (e.g., elderly age, dark skin, latitude, smoking, obesity).	0.10-1.31 in individual trials (I^2=66%; *P*=0.01) Funnel plot and Egger's test results were consistent w/ publication bias. *Subgrp analyses (study-level data):* VitD deficient vs not deficient: OR=0.53 (CI, 0.39-0.72) vs OR=0.90 (CI, 0.81-0.99) (*P*=0.00) Coadministration of calcium: VitD+calcium had greater effect compared w/ calcium alone (OR=0.63; CI, 0.50-0.81) than compared w/ placebo (OR=0.83; CI, 0.72-0.93) and greater placebo-controlled effect (OR=0.83) than vitD alone (OR=0.97; CI, 0.84-1.11) (global *P*=0.01). NOTE: vitD alone had NS effect. Other: No sig interaction of tx w/ community vs institution, intramuscular vs oral, documented increase in serum 25-OHD, D2 vs D3, adherence, high dose (>800 IU/day), and study quality. *Sensitivity analyses:* Using fixed effects model, changing primary outcome to # falls, and changing definition of high vitD dose to ≥800 IU/day or ≥600 IU/day did not change conclusions. *Authors' conclusions:* VitD combined w/ calcium reduces the risk of falls in a population consisting primarily of elderly women.	reasonable. Lack of differential effectiveness according to whether BL serum levels increased suggests that monitoring vitD levels is not necessary, at least in elderly women. *Quality of available evidence according to Murad et al.:* Allocation concealed in 18 trials, double blinding in 18, mean loss to f/u 10% (NR in 9 trials); commercial funding in 34% of studies. Moderate statistical heterogeneity. Results may not be generalizable to populations w/ lower BL risk of falls or adequate vitD status. *Limitations of the SR:* No serious limitations; no analysis by tx duration.
Winzenberg et al. (2011)	6 RCTs (1213 participants)	MA (fixed effects model w/	*Main effects:* Forearm, 0.04; hip bone,	VitD supplementation w/

Review Identification/Outcome of Interest	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality
University of Tasmania, Hobart, Tasmania; Southern Cross University, Coffs Harbour, Queensland, Australia (based on a 2010 Cochrane Review) SR and MA to determine effectiveness of vitD supplementation for improving BMD in healthy children and adolescents and to identify effect modifiers *Databases searched:* CCRCT, MEDLINE, Embase, CINAHL, AMED, ISI Web of Science (conference abstract issues of key journals for 2007-2008 were also searched) *Search time frame:* To August 9, 2009 *Included studies:* All 3 studies included in Chung 2009 plus Dukas 2004, El-Hajj 2006 (boys), and Viljakainen 2006	*Population of interest:* Children and adolescents *Intervention of interest:* VitD w/ or w/o calcium *Outcome of interest:* BMD *Study inclusion/exclusion criteria:* NR other than lack of language restriction *Study characteristics:* 100% girls in 5 studies; mix of prepubertal and pubertal, mean age 10-13 yrs; BL 25-OHD 7.3-47 nmol/L; vitD dose 132-2000 IU/day	exploration of statistical heterogeneity). BMD outcomes were converted to SMD of % change from BL. *Quality assessment:* Sequence generation, allocation concealment, blinding, loss to f/u or other missing data, publication bias	0.06; total body, 0.10, lumbar spine, 0.15. All effects were NS but effect on lumbar spine showed trend toward significance (CI, –0.01 to 0.31; *P*=0.007). *Subgrp analyses:* VitD dose >200 IU/day vs ≤200 IU/day: No difference in effects Girls vs boys: NS between-subgrp difference; SMD in girls 0.13-0.20, all NS except for lumbar spine; SMD in boys, –0.07 to 0.01, all NS. BL 25-OHD: NS between-subgrp differences; larger but generally NS w/in-subgrp effects w/ BL <35 nmol/L. Pubertal status and compliance: Trend toward significant (*P*=0.09) difference favoring prepubertal status and high compliance. Pubertal status: NS w/in-grp and between-grp differences. Data were insufficient to allow analysis by ethnicity or sun exposure. *Adverse events:* Studies reported a low rate of events, most of which were not obviously related to supplementation. There was 1 incidence of increased calcium levels but no instance of hypercalcemia. *Authors' conclusions:* It is unlikely that vitD supplements are beneficial in children and adolescents w/ normal vitD levels.	or w/o calcium was not effective in improving BMD in older children and adolescents. *Quality of evidence according to Winzenberg et al.:* Sequence generation and allocation concealment adequately described in half of studies, all double-blinded, no serious loss to f/u, no publication bias suggested by funnel plots. *Limitations to SR:* None noted.

APPENDIX IV. Vitamin D Supplementation and Nonskeletal Health Outcomes in Healthy Populations: Findings from Randomized Controlled Trials (RCTs)

Key: 25-OHD, 25-hydroxyvitamin D; ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CI, 95% confidence interval; CLIA, Chemiluminescence immunoassay; CPBA, competitive protein binding assay; CRC, colorectal cancer; CVD, cardiovascular disease; EIA, enzyme immunoassay; f/u, follow-up; g, gram; GHQ, General Health Questionnaire; grp(s), group(s); HbA1C, glycated hemoglobin; HPLC, high-pressure liquid chromatography; HR, hazard ratio; hx, history; ITT, intention-to-treat; IU, international units; MCS, mental component score of SF-12; µg, microgram; MI, myocardial infarction; mm Hg, millimeter of mercury; nmol, nanomole; NR, not reported; NS, not statistically significant; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; pt(s), patient(s); RIA, radioimmunoassay; RR, relative risk; SD, standard deviation; TIA, transient ischemic attack; tx, treatment; URI, upper respiratory infection; vit, vitamin; WHI, Women's Health Initiative; wt, weight

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
Maxwell et al. (1981); Brooke et al. (1980) St. George's Hospital, London, UK *F/u:* Outcomes assessed at delivery *Latitude:* NR *Season:* All (2-yr study)	n=126 expectant women randomized to vitD (n=59; mean age 23.9±4.8 yrs; 25-OHD 20.2 nmol/L) or placebo (n=67; mean age 23.7±3.1 yrs; 25-OHD 20.0 nmol/L) *Inclusion criteria:* Asian immigrants; no preterm deliveries, congenital malformations, or maternal illness likely to affect fetal growth	Calciferol 1000 IU/day or placebo beginning 28-32 wks gestation until delivery; double-blinding CPBA χ^2 test *Outcome measures:* Maternal wt gain; newborn length, wt, and head circumference; newborn fontanel area	Mean maternal daily wt gain: 63.3±2.6 g in vitD grp and 46.4±3.6 g in placebo grp (P<0.001) *Newborn anthropometry (vitD; placebo):* Birth wt (g): 3157±61; 3034±64 (NS) Crown-heel length (cm): 49.7±0.3; 49.5±0.4 (NS) Head circumference (cm): 34.5±0.1; 34.3±0.2 (NS) Fontanel area (cm^2): 4.1±0.4; 6.1±0.7 (P<0.05) *Adverse effects:* None	Results suggest that supplementation w/ vitD during the last trimester of pregnancy improves maternal wt gain and decreases fontanel area of newborn. *Limitations:* Randomization method NR; method of allocation concealment NR. *Quality:* Good
Nilas and Christiansen (1984) University of Copenhagen, Copenhagen, Denmark *F/u:* 1 or 2 yrs *Latitude:* NR *Season:* All (1- or 2-yr study)	n=238 women in 3 placebo-controlled trials: Trial A (n=151; 45-54 yrs of age; 2-yr duration), Trial B (n=44; 47-56 yrs of age; 1-yr duration), or Trial C (n=43; 70 yrs of age; 1-yr duration); BL 25-OHD NR *Inclusion criteria:* Postmenopausal women	All participants received calcium 500 mg/day+vitD 2000 IU; calcitriol 0.25 µg or 0.5 µg; alfacalcidiol 0.25 µg; or placebo/day; double-blinding Student's *t*-test *Outcome measures:* Body wt	*% of initial body wt at f/u:* VitD3: 98.7%±3.1% Alfacalcidiol 0.25 µg: 100.0%±2.9% Calcitriol 0.25 µg: 100.1%±3.2% Calcitriol 0.5 µg: 100.0%±1.7% Placebo: 99.6%±2.8% Study results were pooled across studies for the subgrp women who	Results suggest that supplementation w/ vitD or vitD analogs has no effect on body wt. *Limitations:* Entry criteria NR; participant characteristics NR; randomization method NR; method of allocation concealment NR; lack of vitD only grp.

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			were overwt; there were no differences in wt change between placebo and vitD grps. *Blood glucose:* Very small w/in-grp changes; NS between-grp differences *Adverse effects:* NR	*Quality:* Fair
Mallet et al. (1986) Hospital Charles Nicolle, Rouen, France *F/u:* Outcomes assessed at delivery *Latitude:* NR (Northwestern France) *Season:* Winter	n=77 expectant women randomized to daily vitD (n=21; mean age 26 yrs, range 18-35); single dose vitD (n=27; mean age 25 yrs, range 19-36); or control grps (n=29; mean age 25 yrs, range 18-35); BL 25-OHD NR *Inclusion criteria:* Expectant mothers; term pregnancies delivered in February or March	Participants in tx grps received either vitD2 1000 IU daily for last 3 mos of pregnancy or a single dose of vitD2 200,000 IU in 7th mo; control participants had no intervention CPBA Mann-Whitney, Wilcoxon *Outcome measures:* Newborn wt	*Mean birth wts (g):* Daily vitD: 3370±80 Single dose vitD: 3210±90 Control: 3460±70 (differences between grps were NS) *Adverse effects:* NR	Results suggest that supplementation w/ vitD during late pregnancy has no effect on birth wt. *Limitations:* Randomization method NR; method of allocation concealment NR; minimal participant characteristics. *Quality:* Good
Marya et al. (1988) Medical College Hospital, Rhotak, India *F/u:* Outcomes assessed at delivery *Latitude:* NR *Season:* NR	n=200 expectant women randomized to vitD (n=100; mean age 24.0±3.7 yrs; vitD intake 35.0±7.1 IU/day) or control (n=100; mean age 24.1±3.2 yrs; vitD intake 35.7±6.2 IU/day); BL 25-OHD NR *Inclusion criteria:* Expectant mothers, 22-35 yrs of age; no complications such as preeclampsia, antepartum hemorrhage, or preterm delivery; no twin pregnancies	VitD3 600,000 IU/mo to mother during 7th and 8th mos of gestation; control grp received no supplementation Z test, χ^2 test *Outcome measures:* Newborn length, wt, and head circumference	*Newborn anthropometry (vitD; control):* Birth wt (kg): 2.99±0.36; 2.8±0.37 Crown-heel length (cm): 50.06±1.79; 48.45±2.04 Head circumference (cm): 33.99±1.02; 33.41±1.11 (all analyses *P*<0.001) Incidence of low birth wt was 4% in vitD grp and 19% in non-supplemented grp (significance NR). In subgrp analysis of women w/ similar wt gain, newborn birth wt was significantly greater in vitD grp (2.95±0.17 kg) than non-supplemented grp (2.76±0.25 kg)	Results suggest that supplementation w/ vitD during the last trimester of pregnancy improves newborn size and wt compared w/ no supplementation. *Limitations:* Randomization method NR; study duration NR; method of allocation concealment NR; not all data presented in numerical format; statistical methods NR; slight differences between grps were reported as highly significant by authors. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			(*P*<0.01). *Adverse effects:* No evidence of hypercalcemia	
Harris and Dawson-Hughes (1993) Tufts Human Nutrition Research Center on Aging, Boston, MA *F/u:* 1 yr *Latitude:* NR (Boston, MA) *Season:* All (1-yr study)	n=250 participants (mean age 62±5 yrs; current or hx of tx for depression 6%) randomized to vitD or placebo (n=125/grp); BL 25-OHD NR *Inclusion criteria:* Postmenopausal women; white race; good general health; ≥6 mos since last menses; spinal bone density w/in 2 SD of reference mean	All participants received calcium 377 mg/day. Participants received vitD 400 IU/day or placebo. CPBA Friedman's two-way ANOVA, Mann-Whitney test, Spearman's rank order correlation *Outcome measures:* Profile of Mood States questionnaire	There were no differences in mood scores between vitD and placebo grps (data not shown). *Adverse effects:* NR	Results suggest that supplementation w/ vitD has no effect on mood. *Limitations:* Study designed to monitor mood states over different seasons; method of allocation concealment NR; data of vitD supplementation were not shown; lack of vitD only grp. *Quality:* Good
Trivedi et al. (2003) University of Cambridge, Cambridge, England *F/u:* 5 yrs *Latitude:* NR *Season:* All (5-yr study)	n=2686 participants randomized to vitD (n=1345; mean age 74.8±4.6 yrs; hx CVD 29.3%) or placebo (n=1341; mean age 74.7±4.6 yrs; hx CVD 27.4%); BL 25-OHD NR *Inclusion criteria:* 65-85 yrs of age; no vitD supplementation	VitD 3100,000 IU or placebo every 4 mos for 5 yrs; double-blinding (participants and investigators). Participants could continue all drug therapies and were to discontinue the study intervention if their provider recommended supplementation w/ vitD >200 IU/day. ITT, Cox regression *Outcome measures:* All-cause, CVD and cancer mortalities; CVD and cancer incidence	22.8% and 24.2% of participants in vitD and placebo grp, respectively, did not complete 5-yr study (*P*=0.41), including participants who died (w/drawal was 5.7% and 6.2%). *Mortality (vitD; placebo) (age-adjusted RR) (%):* All-cause: 16.7; 18.4 (RR=0.88; CI, 0.74-1.06) CVD: 7.5; 8.7 (RR=0.84; CI, 0.65-1.10) Cancer: 4.7; 5.4 (RR=0.86; CI, 0.61-1.2) (all analyses NS) *Incidence (vitD; placebo) (age-adjusted RR) (%):* CVD: 35.5; 37.5 (RR=0.90; CI, 0.77-1.06) Cancer: 14.0; 12.9 (RR=1.09; CI, 0.86-1.36) *Subgrp analysis according to sex:*	Results suggest that supplementation w/ vitD has no effect on mortality or the incidence of CVD or cancer. *Limitations:* Randomization method NR; method of allocation concealment NR; data obtained via mailed questionnaires; lack of statistical power for main effects; health status based on participant's declarations. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			All RRs remained NS w/in men and women subgrps. Compared w/ RRs for men, RRs for women were higher for CVD, and exceeded 1.00 for cerebrovascular disease; RRs for women were dramatically lower for cancer. However, men-women differences were NS (overlapping CIs). *Adverse effects:* NR	
Dumville et al. (2006) Multiple sites in UK *F/u:* 6 mos *Latitude:* Multiple sites *Season:* Winter and spring	n=2117 participants randomized to vitD (n=912; mean age 77.2±5.2 yrs) or control (n=1205; mean age 76.75±5 yrs); BL 25-OHD NR *Inclusion criteria:* Women ≥70 yrs of age; life expectancy >6 mos; calcium <500 mg/day; and ≥1 of following risk factors : body wt ≤58 kg, prior fracture, family hx of hip fracture, smoker, fair or poor health	Participants received Calcichew D3 tablets (total daily dose: vitD 800 IU; calcium 1000 mg) or no supplement between November and April. ITT, Mann-Whitney test, ANCOVA (adjusted for BL MCS score and age) *Outcome measures:* MCS of SF-12	74.6% of vitD grp and 78.1% of control grp had valid score at both assessment times. Differences between grps mean MCS (100-point scale) at BL (–0.59; CI, –1.51 to –0.33) and 6 mos (1.76; CI, –0.81 to –1.16) were NS. Differences were NS after controlling for BL score and age (–0.49; CI, –1.34 to –0.81). *Adverse effects:* NR	Results suggest that supplementation w/ vitD and calcium has no effect on mental health of elderly women. *Limitations:* Only one mental health scale was used for outcome; lack of vitD only grp; substantial missing data. *Quality:* Fair
Wactawski-Wende et al. 2006 WHI trial *F/u:* Mean 7 yrs *Latitude:* *Season:* Yr-round	n=36,282 women randomized to vitD (n=18,176) or placebo (n=18,106) (85 nmol/L) 300-500 Langleys *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age; predicted survival >3 yrs; vitD <600 IU/day; no current use of oral corticosteroids or hx of renal calculi or hypercalcemia	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day. Double blinding (participants; assessment of CRC cases). Study pills discontinued if daily intake exceeded 1000 IU vitD. DiaSorin Liasion assay ITT, Kaplan-Meier, Cox regression (w/ adjustment for age, hx of CRC, and tx assignment in WHI trials), logistic regression techniques. *Outcome measures:* CRC incidence and mortality; total cancer	Results available for 97% of participants w/in 18 mos before end of study. *Invasive CRC:* HR=1.08 (CI, 0.86-1.4; NS) Similar HRs after exclusion for poor adherence or hx of CRC. NS differences in HRs across subgrps defined by age at screening, race/ethnicity, education, 1st-degree relative w/ CRC, hx of polyp removal, BMI, physical activity, total energy intake, energy from saturated fat, total calcium intake, total vitD	Results suggest that 7 yrs of supplementation w/ vitD at 400 IU/day+calcium has no effect on the proportion of postmenopausal women w/ CRC-related mortality. *Limitations:* Results based on reported cases of CRC; bowel exams not required by protocol so some cancers may have been missed; f/u duration may have been too short considering 10- to 20-yr latency of CRC; lack of a vitD-only grp; low tx dose of vitD compared w/ other studies; a priori definition of symptoms NR.

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
		incidence and mortality	intake, regional solar exposure, multivitamin use, smoking status, NSAID use, and hormone-tx use. *Other outcomes:* Cancer: HR=0.98 (CI, 0.91-1.05; NS) CRC-related mortality: HR=0.82 (CI, 0.52-1.29; NS) Cancer-related mortalilty: HR=0.89 (CI, 0.77-1.03; NS) All-cause mortality: HR=0.91 (CI, 0.8-1.01; NS) Analysis of nested case-control subgrp (306 pairs) revealed a significant interaction between tx grp and BL 25-OHD (*P*=0.02 for trend). . ORs decreased from 1.15 at ≥58.4 nmol/L to 0.7 at <31.0 nmol/L, but all were NS. *Adverse effects:* NS differences in self-reported symptoms, including moderate-severe abdmominal symptoms. For kidney stones, HR=1.17 (CI, 1.02-1.4; *P*=0.02).	*Quality:* Good (Fair for CRC outcomes)
Wagner et al. (2006) Medical University of South Carolina, Charleston, SC *F/u:* 7 mos *Latitude:* NR *Season:* NR	n=19 mothers randomized to vitD (n=9; mean age 28.3±5.9 yrs; 25-OHD 34 ng/mL (85 nmol/L); gestation 39.2±0.7 wks; infant birth wt 3614.2±349.8 g) or placebo (n=10; mean age 30.3±3.3 yrs; 25-OHD 32.2 ng/mL (80 nmol/L); gestation 38.8±1.2 wks; birth wt 3435.6±440.0 g) *Inclusion criteria:* Lactating mothers w/in 1 mo postpartum and their infants; intention to	All mothers had received prenatal supplements containing vitD 400 IU/day. Mothers in vitD grp received additional vitD 6000 IU/day and those in control grp received placebo. Infants of mothers in control grp received vitD 300 IU/day; infants of mother's in vitD grp received placebo. HPLC and RIA ITT, t-test, McNemar's χ^2 test,	10 participants completed the study, 5 dropped out before 5 mos and 4 dropped after 5 mos. # participants analyzed at each time point was NR. *Infant wt (vitD; control) (kg):* 1 mo: 4.6±0.7; 4.7±0.4 4 mos: 6.6±0.8; 6.7±0.5 7 mos: 8.4±1.1; 7.6±0.8 *Infant head circumference (vitD; control) (cm):*	Results suggest that additional vitD supplementation in lactating women, beyond prenatal supplementation, has no effect on infant growth rate. *Limitations:* Convenience sample may not have been large enough to detect differences; all participants received vitD; high rate of dropouts; # participants analyzed at each time point was NR; use of 400 IU/day vitD in placebo grp.

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
	breastfeed ≥6 mos; no diabetes, hypertension, parathyroid disease, and uncontrolled thyroid disease	repeated ANOVA measures *Outcome measures:* Infant wt, length, and head circumference	1 mo: 37.6±1.7; 37.9±1.0 4 mos: 41.2±1.6; 41.7±0.8 7 mos: 43.6±0.9; 44.3±0.9 *Infant length (vitD; control) (cm):* 1 mo: 55.9±2.9; 54.6±1.1 4 mos: 62.8±1.9; 62.4±1.7 7 mos: 69.3±2.9; 65.5±1.8 (all analyses NS) *Adverse effects:* None related to vitD supplementation	*Quality:* Poor
Caan et al. (2007) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round NOTE: Data pertaining to obese subgrps are presented in Appendix Vb.	n=36,184 participants randomized to vitD (n=18,176; BMI, 28.9±6; total vitD intake, 9±7 µg) or placebo (n=18,106; BMI, 28.8±6; total vitD intake, 9±7 µg); BL 25-OHD NR 22,827 (63%) of women were of normal wt or overwt. 13,189 (36%) were obese. *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; double-blinding (participants and staff); study medication discontinued after report of kidney stones, hypercalcemia, dialysis, calcitriol use, or personal supplementation of vitD >1000 IU/day. ITT, linear repeated-measures regression modeling, nominal multinomial logistic regression modeling *Outcome measures:* Body wt	Participants in vitD grp had smaller annual wt gains than those in placebo grp (mean difference –0.13 kg, range –0.21 to –0.05; *P*=0.001). *Mean difference in wt change according to BL BMI (kg/m^2) (kg) (range):* <25: –0.08 (–0.23 to 0.06) 25 to <30: –0.09 (–0.22 to 0.04) 30 to <35: –0.23 (–0.4 to –0.06) ≥35: –0.17 (–0.38 to 0.04) Participants who were heavier (i.e., higher BMI) had a greater tx effect (*P*=0.04 for interaction). Tx effects did not vary for other BL characteristics, including ethnicity, age, education level, waist circumference, total calcium and vitD intake, energy intake, smoking, physical activity, and fruit and vegetable intake. *Odds of wt gain after 3 yrs in study (1-3 kg gain; >3 kg gain):*	Results suggest that supplementation w/ vitD and calcium reduces the wt gain associated w/ early menopause. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; low tx dose of vitD; method of allocation concealment NR. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			Effect of calcium+vitD: OR=0.95 (CI, 0.90-1.01); OR=0.94 (CI, 0.90-0.99) (*P*=0.05 for interaction) Calcium <1200 mg: OR=0.89 (CI, 0.83-0.96); OR=0.89 (CI, 0.84-0.95) Calcium >1200 mg: OR=1.05 (CI, 0.96-1.15); OR=1.01 (CI, 0.93-1.10) (total calcium intake *P*=0.008 for interaction) *Adverse effects:* NR	
Hsia et al. (2007) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=36,282 participants randomized to vitD (n=18,176; mean age 62.4±7 yrs; BMI, 29.1±5.9) or placebo (n=18,106; mean age 62.4±6.9 yrs; BMI, 29.0±5.9); BL 25-OHD NR *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; double-blinding. Personal supplementation w/ vitD3 ≤400 IU/day was allowed. ITT, Cox proportional hazards models (stratified according to age, prevalent CVD, tx assignment in hormone tx or diabetes mellitus trials); tests for interaction between tx and subgrp factor. All HRs adjusted for age and prevalent CAD at BL. *Outcome measures:* Events related to CAD	*Main effects:* MI or CAD death: HR=1.04 (CI, 0.92-1.18) Stroke: HR=0.95 (CI, 0.82-1.10) Risk of coronary revascularization, hospitalized heart failure, confirmed angina, TIA, and composite outcomes were similar between grps. *Effect on MI or CAD death by BMI subgrp:* <25 kg/m^2: HR=1.16; ≈CI, 0.8-1.5 25-<30 kg/m^2: HR=1.18; ≈CI, 0.9-1.5 ≥30 kg/m^2: HR=0.91; ≈CI, 0.7-1.2 (*P*=0.04 for interaction) *Effect on MI or CAD death by other subgrps:* NS test for interaction for age, waist circumference, medication use, CVD risk factors or CVD at BL, and calcium/vitD intake at BL. *Effect on stroke by use of anticholesterol medication:* Yes, HR=0.69 (≈CI, 0.5-1.0); no, HR=1.04 (≈CI, 0.8-1.5) (*P*=0.04 for	Results suggest that supplementation w/ vitD and calcium has NS effect on coronary and cerebrovascular events in postmenopausal women. *Limitations:* Allowed personal intake of vitD dose same as tx dose used in study; therefore, participants in placebo grp may have had same vitD intake as those in tx grp; method of allocation concealment NR; low vitD tx dose. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			interaction) *Effect on stroke by CAD risk factors:* None, HR=1.14 (≈CI, 0.7-1.6); 1-2, HR=0.9 (≈CI, 0.7-1.1); ≥3, HR=0.76 (≈CI, 0.3-2.2) (*P*=0.02 for interaction) *Effect on stroke by use of statin at BL:* Yes, HR=0.54 (≈CI, 0.2-0.9); no, HR=1.0 (≈CI, 0.8-1.2) (*P*=0.04 for interaction) *Effect on CAD or stroke by calcium or vitD intake at BL:* No interaction *Adverse events:* NR	
Lappe et al. (2007) Creighton University, Omaha, NE *F/u:* 4 yrs *Latitude:* 41.4°N *Season:* All (4-yr study)	n=1179 participants (mean age 66.7±7.3 yrs; BMI 29.0±5.7) randomized to vitD (n=446; 25-OHD 72.1±20.7 nmol/L), calcium (n=445; 25-OHD 71.6±20.5 nmol/L), or placebo (n=288; 25-OHD 71.8±20.0 nmol/L) *Inclusion criteria:* Postmenopausal women; >55 yrs of age; no cancer; sufficient mental and physical status to participate in 4-yr study	Participants received calcium (1400 mg calcium citrate or 1500 mg calcium carbonate), vitD 1000 IU+calcium, or placebo; double-blinding RIA ITT, logistic regression models developed w/ use of intervention, BL 25-OHD, 12-mo 25-OHD, BMI, and age. *Outcome measures:* Cancer incidence	86.8% of participants completed study. *Cancer incidence (vitD; calcium; placebo) (# pts):* Yrs 1-4: 13; 17; 20 Yrs 2-4: 8; 15; 18 VitD and calcium grps had lower incidence of cancer compared w/ placebo grp (*P*<0.03). Cancer risk in vitD and calcium grps, RR=0.402 (CI, 0.20-0.82; *P*=0.013) and RR=0.532 (CI, 0.27-1.03; *P*=0.006), respectively. Cancer risk after yr 1, RR=0.232 (CI, 0.09-0.60; *P*<0.005) in vitD grp and unchanged in calcium grp. Logistic regression revealed that tx assignment was an independent predictor of cancer incidence after adjustment for 12-mo 25-OHD	Results suggest that supplementation w/ vitD and calcium, or calcium alone, reduces the incidence of cancer in postmenopausal women. *Limitations:* Lack of a vitD only grp; method of allocation concealment NR. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			(*P*<0.03) independent determinant of cancer risk. Cancer risk per unit concentration of serum 25-OHD at BL, RR=0.983 (CI, 0.968-0.997; *P*<0.01) after adjustment for tx; 35% reduced risk of cancer for every 25 nmol/L increase in serum 25-OHD. No subgrp analysis or test for interaction between tx and BL 25-OHD level. *Adverse effects:* No serious tx-related adverse events. Renal calculi in 1 participant in placebo grp, 1 participant in vitD grp, and 3 participants in calcium grp.	
Chlebowski et al. (2008) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=36,282 participants randomized to vitD (n=18,176) or placebo (n=18,106) Nested case-control subgrp (n=1067 pairs) resulted in 895 evaluable participants in vitD grp (25-OHD 50.0 nmol/L) and 898 evaluable in placebo grp (25-OHD 52.0 nmol/L) Dietary and supplementary intake of vitD was similar in both grps. *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age; predicted survival >3 yrs; no breast cancer; no other cancer w/in 10 yrs of study	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; blinding (participants and staff); study medication discontinued after report of kidney stones, hypercalcemia, dialysis, calcitriol use, or personal supplementation of vitD >1000 IU/day. CLIA (DiaSorin Liaison) ITT, Cox proportional hazards models (stratified according to age, prevalent disease, tx assignment in hormone therapy or diabetes mellitus trials), Kaplan-Meier estimates, Fisher's exact test, *t*-test, χ^2 test *Outcome measures:* Breast cancer incidence and mortality	Breast cancer in 668 participants (0.52%) in vitD grp and 693 participants (0.54%) in placebo grp (HR=0.96; CI, 0.85-1.09). Tumor size was 1.54 cm in vitD grp and 1.71 cm in placebo grp (*P*=0.05). There were 23 cancer-related mortalities in each grp. Cancer stage and histology were similar between grps. Effect of BL vitD intake: Participants in highest quartile had more breast cancer in vitD than placebo grp (HR=1.34; CI, 1.01-1.78) and those in lowest quartile had fewer breast cancers in vitD than placebo grp (HR=0.79; CI, 0.65-0.97) (*P*=0.003 for interaction). However, there were no significant interactions in the nested case-control analyses between BL characteristics, including serum 25-OHD, and tx	Results suggest that supplementation w/ vitD and calcium has no effect on the incidence of breast cancer in postmenopausal women. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; method of allocation concealment NR; low tx dose of vitD; f/u duration was too short to detect all cases of breast cancer. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			assignment, after adjustment for other factors. Logistic regression analysis of nested case-control subgrp adjusted for age, race, latitude, breast cancer family hx, prior breast biopsies, hormone tx, and participation in hormone tx or diabetes mellitus trials revealed that higher BL 25-OHD levels were associated w/ lower breast cancer risk (*P*=0.04). This association was lost when analyses further adjusted for BMI and physical activity (*P* trend=0.2) *Adverse effects:* Minimal	
de Boer et al. (2008) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=33,951 participants randomized to vitD (n=16,999) or placebo (n=16,952); BL 25-OHD NR Dietary and supplementary intake of vitD was similar in both grps. *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age; no diabetes	Participants received total dose of vitD 400 IU and 1000 mg calcium or placebo/day; double-blinding. Personal supplementation w/ vitD ≤1000 IU/day was allowed. ITT, Cox proportional hazards models (stratified by age and participation in other WHI trials), *t*-test; test for interaction between tx and subgrp factors *Outcome measures:* Diabetes incidence	*Main effect* Unadjusted: HR=0.97 (CI, 0.86-1.09) Adjusted for nonstudy use of calcium or vitD: HR=1.01 (CI, 0.94 to 1.10) (overlapping CIs indicate NS difference in the 2 HR estimates) *Effect according to pt factors:* NS interaction w/ age, race/ethnicity, education, family hx of diabetes, calcium intake at BL (trend toward significance), vitD intake at BL, multivitamin use, alcohol intake, smoking, sun exposure, physical activity, BMI, waist circumference, hormone tx at BL, FPG, metabolic syndrome, 25-OHD level (<32.2/32.2-43.6/43.7-60.1/≥60.2 nmol/L; no clear pattern in variation of HRs)	Results suggest that supplementation w/ vitD+calcium has no effect on the incidence of diabetes in postmenopausal women. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; method of allocation concealment NR; low tx dose of vitD. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			Adverse effects: NR	
Margolis et al. (2008) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=36,282 participants randomized to vitD (n=18,176) or placebo (n=18,106) Dietary and supplementary intake of vitD was similar in both grps. *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age; no hypertension; predicted survival >3 yrs; no use of corticosteroids or calcitriol	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day. Personal supplementation w/ vitD ≤1000 IU/day was allowed. CLIA (DiaSorin Liaison) ITT, linear repeated-measures regression modeling, Cox proportional hazards models (stratified by age and participation in other WHI trials) *Outcome measures:* BP, hypertension incidence	By end of study, systolic BP declined by 1 mm Hg and diastolic by 4 mm Hg; however, differences between grps was NS. No subgrps, including demographic characteristics, hypertension risk factors, calcium and vitD intake, and 25-OHD levels, had a significant change in BP associated w/ vitD tx. Hypertension developed in 3377 participants (19.6%) in vitD grp and 3315 participants (18.3) in placebo grp (HR=1.01; CI, 0.96-1.06). *Tx effect by BL 25-OHD:* <34.4 nmol/L, HR=1.52 (CI, 0.89-2.59); 34.4-47.6 nmol/L, HR=1.48 (CI, 0.89-2.46); 47.7-64.6 nmol/L, HR=1.15 (CI, 0.69-1.92); ≥64.7 nmol/L, HR=0.79 (CI, 0.51-1.22) (*P*=0.01 for interaction) *Adverse effects:* NR	Results suggest that supplementation w/ vitD+calcium has no effect on blood pressure or hypertension in postmenopausal women. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; method of allocation concealment NR; lack of a vitD-only grp; low tx dose of vitD. *Quality:* Good
Daly and Nowson (2009) University of Melbourne, Melbourne; Deakin University, Melbourne, Australia *F/u:* 2 yrs *Latitude:* NR *Season:* Yr-round	n=167 participants randomized to vitD (n=85; mean age 61.3±7.7 yrs; BMI 26.2±3.3 kg/m^2; BL 25-OHD 78±23 nmol/L) or control (n=82; mean age 61.2±7.5 yrs; BMI 26.7±3.2 kg/m^2; 67±23 nmol/L) *Inclusion criteria:* Caucasian men; >50 yrs of age; BMI <35 kg/m^2; no vitD supplements in preceding 12 mos; no resistance training in preceding 6 mos; no hx of	Participants received milk fortified w/ vitD 400 IU and calcium or no additional milk RIA (DiaSorin) ITT, *t*-test, χ^2 test *Outcome measures:* Body wt, BP	10.8% of participants w/drew from study. Wt change (kg) (vitD; control): 6 mos: 0; –0.3 12 mos: 0.5; 0.1 18 mos: 0; –0.7 24 mos: 0.6; 0.1 There was no significant effect of supplementation in subgrp who had BL 25-OHD levels <75 nmol/L.	Results suggest that supplementation w/ vitD+calcium has no effect on body wt or BP in healthy men. *Limitations:* Some participants were taking antihypertensive agents; relatively healthy population so extrapolation to other populations is not possible; milk was fortified w/ additional nutrients that were not controlled

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
	osteoporotic fracture; no disease or medication known to affect bone metabolism		*Adverse effects:* 5 participants w/drew from study because of gastrointestinal side effects	for; post hoc analysis revealed that sample size not large enough to detect tx effect. *Quality:* Fair
LaCroix et al. (2009) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=36,282 participants randomized to vitD (n=18,176; mean age 62.4±7 yrs) or placebo (n=18,106; mean age 62.4±6.9 yrs) Dietary and supplementary intake of vitD was similar in both grps. BL 25-OHD in nested case-control sample (% participants): <35.4 nmol/L (41%), 35.4-52.4 nmol/L (31%), >52.4 nmol/L (28%) *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age; predicted survival >3 yrs; no use of corticosteroids or calcitriol	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day Personal supplementation w/ vitD ≤1000 IU/day was allowed. CLIA (DiaSorin Liaison) ITT, Cox proportional hazards models (stratified by age and participation in other WHI trials), logistic regression *Outcome measures:* All-cause mortality, cause-specific mortality	There were 744 mortalities in vitD grp and 807 in placebo grp (HR=0.91; CI, 0.83-1.01). HRs close to unity for specific causes of mortality, including stroke, cancer, CAD, and other causes. HRs for total mortality, CVD death, CAD death, cerebrovascular death, cancer death, and other/I death were similar in subgrps defined by age (<70 vs ≥70 yrs).Interaction by ethnicity, calcium use, total calcium intake, total vitD intake, latitude, BL blood pressure, smoking status, physical activity, CVD risk, BMI, hx of CVD, # chronic conditions, and self-reported health status w/ tx was NS for effect on total mortality. Nested case-control analysis (n=323) suggested a protective effect (OR=0.79; NS) in the subgrp w/ BL 25-OHD <35.4 nmol/L and a harmful effect (NS) in the higher tertiles of BL 25-OHD. NS interaction. Subgrp analysis suggested greater reduction in total mortality for adherent women w/in <70 yrs age grp. *Adverse effects:* NR	Results suggest that supplementation w/ vitD+calcium may have a protective effect on mortality rates in postmenopausal women. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; low tx dose of vitD. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
Brunner et al. (2011) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=34,670 eligible participants; vitD (n=17,343) or placebo (n=17,3327); BL 25-OHD NR Dietary and supplementary intake of vitD was similar in both grps. *Inclusion criteria:* Postmenopausal women; 50-70 yrs of age; predicted survival >3 yrs; no use of corticosteroids or calcitriol; no hx of invasive cancer *Exclusion criteria (for this analysis):* Hx of invasive cancer	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; double-blinding. Personal supplementation w/ vitD ≤1000 IU/day was allowed. ITT, χ^2 test, Wald statistic, Cox proportional hazards models, Kaplan-Meier; Bonferroni's tests of significance *Outcome measures:* Invasive cancer incidence and mortality	Invasive cancer in 1306 participants (7%) in vitD grp and 1333 participants (7.4%) in placebo grp (HR=0.98; CI, 0.9-1.05; *P*=0.54). There were no differences between grps for the incidence of specific invasive cancers. Similar HR after omission of nonadherent participants from analysis. Cancer mortality in 315 participants (1.7%) in vitD grp and 347 participants (1.9%) in placebo grp (HR=0.9; CI, 0.77-1.05). Greater protective tx effect in participants w/o first-degree relative w/ cancer and in past smokers (significant interaction). Harmful effect (HR=1.22; 95% CI, 1.02-1.45) when total vitD intake at BL was ≥ 600 IU/day; NS protective or neutral effects at lower levels of BL intake (*P*<0.04 for tx-intake interaction). There was a greater incidence of invasive cancers in vitD grp for participants in highest quartile of total vitD intake (HR=1.22; CI, 1.02-1.45; *P*<0.04). Age, ethnicity, education, BMI, physical activity, caloric intake, calcium intake, latitude, solar irradiation, alcohol intake, and current smoking status were not associated w/ the rate of invasive cancer.	Results suggest that supplementation w/ vitD and calcium has no effect on the incidence of invasive cancer or cancer mortality in postmenopausal women. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; low tx dose of vitD; f/u duration may not have been long enough to see tx effect in cancer. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			Adverse effects: NR	
Kumar et al. (2011) Safdarjung Hospital, New Delhi, India *F/u:* 6 mos *Latitude:* 29°N *Season:* Yr-round	n=2079 low-birthwt infants randomized to vitamin D (n=1039; mean birth wt 2.2±0.2 kg; 488 boys, 551 girls) or placebo (n=1040; mean birth wt 2.2±0.2 kg; 482 boys, 558 girls); BL 25-OHD NR *Inclusion criteria:* Singleton infants; ≥37 wks gestation; birth wt 1.8-2.5 kg; <48 hrs of age; no severe congenital abnormalities or expected life span <7 days	VitD3 1400 IU/day or placebo beginning at 7 days of age until 6 mos of age; double-blinding RIA ITT; Weibull regression w/ gamma shared frailty; linear regression; adjustments for BL z score, sex, socioeconomic status, family type, maternal education, breastfeeding status, season, and exposure to sunlight *Outcome measures:* Rate of hospitalization or death, anthropometric measurements	*Participation (vitamin D grp; placebo grp) (% pts):* Dosed: 93.2%; 92% Morbidity data of randomized infants: 72%; 72% Morbidity data of dosed infants: 76%; 78% Anthropometric data of randomized infants: 61%; 62% Anthropometric data of dosed infants: 65%; 68% *Anthropometric z scores (vitD minus placebo grp) (adjusted difference):* Wt: 0.1 (95% CI, 0.01-0.22; *P*=0.026) Length: 0.12 (95% CI, 0.02-0.21; *P*=0.014) Head circumference: –0.08 (95% CI, –0.17 to 0.01; *P*=0.08) Arm circumference: 0.11 (95% CI, 0.01-0.21; *P*=0.033) Hospital admission or death occurred at a rate of 0.22 and 0.23/child yr in vitamin D and placebo grps, respectively. Difference was NS even after adjusting for BL variables. Severe morbidity occurred at a rate of 0.41 and 0.49/child yr in	Results suggest that supplementation w/ vitamin D improved growth according to most measures in low-birthwt term infants, but there was no effect on general health. *Limitations:* Large loss to f/u, and compared w/ overall study grp, infants lost to f/u came from poorer families w/ less parental education; f/u period may have been too short to allow assessment of health outcomes. *Quality:* Good

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
			vitamin D and placebo grps, respectively. Difference was NS even after adjusting for BL variables. *Adverse events:* NR	
Sanders et al. (2011) University of Melbourne, Melbourne; Geelong Monash University, Geelong, Australia *F/u:* 3-5 yrs *Latitude:* 38° S *Season:* Yr-round	n=2258 women randomized to vitD (n=1131) or placebo (n=1127) Biochemical substudy: VitD grp (n=61; median age 74.5 yrs, range 72.6-77.9; 25-OHD 53 nmol/L) and placebo grp (n=57; median age 75 yrs, range 72.9-80.4; 25-OHD 45 nmol/L) *Inclusion criteria:* Women ≥70 yrs of age; risk for hip fracture; risk for low vitD and osteoporosis; vitD supplementation <400 IU/day	Participants received single dose of vitD 500,000 IU or placebo/yr during autumn or winter; double-blinding (participants and staff). ITT, *t*-test, Wald test DiaSorin *Outcome measures:* GHQ, SF-12 A subgrp (n=118; vitD, n=61; placebo, n=57) also analyzed by World Health Organization Well-Being Index; Patient Global Impression Improvement scale	10.2% of vitD grp and 9.8% of placebo grp w/drew from study. *Overall SF-12 scores (vitD; placebo):* Physical score: 41.4; 41.2 Mental score: 52.5; 52.6 (all analyses NS) *Overall GHQ score ≥3 (vitD; placebo) (% pts):* BL: 14%; 15% 12 mos: 13.8%; 13.7% 15 mos: 17.7%; 16.9% (all analyses NS) *Adverse effects:* NS difference in # serious adverse events between grps; no serious adverse events were tx related.	Results suggest that supplementation w/ vitD has no effect on mental well-being. *Limitations:* Outcome measures not completed by all participants; vitD grp had higher rate of falls and fractures than placebo grp, which could have an impact on mental well-being. *Quality:* Good
Grimnes et al. (2011) University of Tromsø, Tromsø; University Hospital of North Norway, Tromsø, Norway *F/u:* 6 mos *Latitude:* NR *Season:* Yr-round	n=104 participants randomized to vitD (n=51) or placebo (n=53) Evaluable participants: VitD grp (n=49; mean age 51.5±8.8 yrs; 25-OHD 42.2±13.0 nmol/L) and placebo grp (n=45; mean age 52.7±9.7 nmol/L; 25-OHD 39.2±12.1 nmol/L) *Inclusion criteria:* Adults 30-75 yrs of age; low serum 25-OHD; nondiabetic; no cancer, steroid	Participants received vitD 20,000 IU or placebo twice/wk; double-blinding (participants, staff, researchers). Electrochemiluminescence immunoassay (Modular E170) ITT, *t*-test, χ^2 test, ANCOVA models adjusting for BL value *Outcome measures:* HbA1C	3.9% of vitD grp and 15% of placebo grp not included in analyses. *Serum HbA1C (vitD; placebo) (% pts):* BL: 5.5%; 5.44% 6 mos: 5.64%; 5.64% (differences between grps NS) *Adverse effects:* NS difference in # adverse effects between grps	Results suggest that supplementation w/ vitD has no effect on HbA1C levels in adults. *Limitations:* Study lacked the power to detect small differences between grps. *Quality:* Fair

Authors	Study Population	Treatment	Results	Conclusions/Comments/ Limitations/Quality
	use, high blood pressure, MI or stroke			
Tang et al. (2011) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=36,282 participants randomized to vitD (n=18,716) or placebo (n=18,106); BL 25-OHD NR Dietary and supplementary intake of vitD was similar in both grps. *Inclusion criteria:* Postmenopausal women; 50-70 yrs of age; predicted survival >3 yrs; no use of corticosteroids or calcitriol; no cancer in preceding 10 yrs w/ exception of non-melanoma skin cancer	Participants received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; double-blinding. Personal supplementation w/ vitD ≤1000 IU/day was allowed. ITT, χ^2 test, Wald statistic, Cox proportional hazards models, Kaplan-Meier *Outcome measures:* Melanoma incidence, non-melanoma skin cancer incidence	Non-melanoma skin cancer in 1683 participants (9%) in vitD grp and 1655 participants (9.1%) in placebo grp (HR=1.02; CI, 0.95-1.07). Subgrp analyses did not show differential effect on risk of non-melanoma skin cancer according to age, BMI, total vitD intake, solar radiation, or hx of cancer, melanoma, or non-melanoma skin cancer. Melanoma in 82 participants (0.4%) in vitD grp and 94 participants (0.5%) in placebo grp (HR=0.86; CI, 0.64-1.16; *P*=0.32). Participants w/ hx of non-melanoma skin cancer had 57% fewer melanomas in the vitD grp compared w/ placebo grp (HR=0.43; CI, 0.21-0.9; *P*=0.038 for interaction). Subgrp analyses did not show differential effect on risk of melanoma according to age, BMI, total vitD intake, solar radiation, or hx of cancer or melanoma. *Adverse effects:* NR	Results suggest that supplementation w/ vitD+calcium has no effect on the incidence of skin cancers. *Limitations:* High level of personal vitD supplementation was allowed; therefore, participants in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; method of allocation concealment NR; low tx dose of vitD; study may have insufficient power to detect differences between grps for a low-incidence disease; f/u duration may not have been long enough to see tx effect in cancer. *Quality:* Good

*According to online calculator: http://hedwig.mgh.harvard.edu/sample_size/size.html.

APPENDIX Va. Vitamin D Supplementation in Individuals with Chronic Disease: Findings from Systematic Reviews

Key: 25-OHD, 25-hydroxyvitamin D; AHRQ, Agency for Healthcare Research and Quality; BL, baseline; BMD, bone mineral density; BP, blood pressure; CI, confidence interval; CV(D), cardiovascular (disease); DFS, disease-free survival; DM, diabetes mellitus; DFS, disease-free survival; (D/S)BP, (diastolic/systolic) blood pressure; FPG, fasting plasma glucose; f/u, follow-up; HbA1C, glycated hemoglobin; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HRT, hormone replacement therapy; HTN, hypertension; hx, history; ITT, intention-to-treat; IU, international units; MA, meta-analysis; µg, microgram; mm Hg, millimeter of mercury; nmol, nanomole; NR, not reported; NS, (statistically) nonsignificant; OS, overall survival; pt(s), patient(s); RCT, randomized controlled trial; RFS, relapse-free survival; SMD, standard mean difference (effect size); TTP, time-to-progression; SR, systematic review; tx, treatment; vitD, vitamin D

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
Musculoskeletal Health				
Hayes (2012) Health technology assessment of vitamin D supplementation for pts w/ osteoporosis *Databases searched:* MEDLINE *Search time frame:* 2002 – July 2012 *Funding source:* Self-funded Included RCTs: Ringe 2001/Ringe 2004, Gutteridge 2003, Iwamotao 2003, Doetsch 2004, Ishida 2004, Shiraki 2004, Matsumoto 2005/Matsumoto 2007, Mizunuma 2006, Nuti 2006, Barone 2007, Hitz 2007, Ringe 2007, Iwamoto 2009, Xia 2009, Bishoff-Ferrari 2010, Felsenberg 2011, Matsumoto 2011, Grimnes 2012	18 RCTs, 3601 participants (17 RCTs and 2547 participants after exclusion of an uncontrolled comparator trial) *Population of interest:* Adults (≥16 years of age) w/ established osteoporosis, osteopenia, or a hx of vertebral fracture or other osteoporosis-related fracture (studies that recruited only pts w/ osteopenia but not osteoporosis were excluded) *Intervention of interest:* VitD (active or inactive) supplementation *Outcomes of interest:* BMD, fractures, falls *Study inclusion criteria:* English language, RCTs *Study exclusion criteria:* Unknown osteoporosis status; risk of	Health technology assessment based on a qualitative SR *Quality assessment:* Internal system similar to GRADE system (but explicit quality ratings were NR)	*VitD3+calcium:* Conflicting results for effect on BMD at different sites; positive effects were small (2 RCTs involving pts w/ hx of fracture). 1 RCT found a pronounced increase in lumbar spine BMD in pts ≤70 yrs of age (0.993±0.131) and a decrease in pts >70 yrs (0.868±0.216; *P*<0.05). *Dose effects (vitD3):* No clear effect (2 RCTs) *Active vitD:* Significant effect on BMD compared w/ no vitD (2 RCTs). More effective than inactive vitD (BMD, fractures, and falls) (2 RCTs). Less effective than bisphophonate (BMD) (4 RCTs). Combination w/ bisphosphonate more effective than either drug alone (BMD and/or fractures and falls, 3 RCTs) Less effective than HRT (1 RCT) Combination w/ HRT more effective than HRT alone (BMD and/or fractures; 2 RCTs) *Authors' conclusions:* Active vitD combined	Authors' conclusions appear to be reasonable. *Limitations of selected evidence according to Hayes:* F/u ≤1 yr in 11 RCTs (limits assessment of effect on on fractures/falls); lack of blinding in many studies; small sample sizes;2 studies were commercially funded; individual study quality ratings NR. *Limitations of the SR:* Authors did not assign a quality rating to bodies of evidence or the overall evidence; BL values of serum 25-OHD NR.

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
	osteoporosis or bone loss due to cancer tx, CVD, rheumatoid arthritis, HIV infection, Crohn's disease, Parkinson's disease, Alzheimer's disease, assessment of vitD+calcium (unless there were a calcium alone arm) *Study characteristics:* Pts were generally vitD deficient and older than age 50 yrs; blinding in 9 RCTs; some studies combined vitD w/ bisphosphonates or HRT; f/u 12 wks to 3 yrs; 1 RCT (Matsumotao 2011) compared 2 different analogs and had no control grp; several studies excluded pts w/ secondary osteoporosis		w/ bisphosphonate is effective; active vitD combined w/ HRT may be effective; insufficient evidence for inactive vitD; no dose-response effect of inactive vitD has been proven.	
Cancer				
Buttigliero et al. (2011) University of Turin, Turin, Italy SR to determine whether hypovitaminosis D is associated w/ poor prognosis and if vitD repletion improves prognosis of cancer pts *Databases searched:* MEDLINE, Embase, ISI Web of Knowledge, The Cochrane Library *Search time frame:* Through June 2010 *Funding source:* NR Included RCTs: Beer 2007, Attia 2008, Scher 2010	3 RCTs, 1273 participants *Population of interest:* Cancer pts *Intervention of interest:* VitD (active or inactive) supplementation *Outcomes of interest:* Primary: OS Secondary: TTP, DFS, RFS *Study inclusion criteria for vitD repletion studies:* English language, RCTs *Study exclusion criteria:* NR *Study characteristics:* All selected RCTs involved pts w/ progressive metastatic androgen-independent	SR, including MA of OS data. *Quality assessment:* Cochrane Collaboration tool for RCTs (sequence generation, allocation concealment, blinding, incomplete outcome data addressed, selective reporting, other bias).	*Adjusted HR (<1 favors vitD):* Beer 2007: 0.67 (CI, 0.45-0.97; *P*=0.07) Scher 2010: 1.33 (*P*=0.19) *Median OS (vitD arm, control) (mos):* Scher 2010: 16.8, 19.9 (significance NR) Attia: 17.8, 16.4 (NS) *Median PFS:* No difference in Attia 2008; NR for other 2 studies. No other outcomes were discussed by Buttigliero et al. *Pooled estimate of RR of death:* Fixed effects model: 1.07 (CI, 0.93-1.23) Random-effects model: 1.00 (CI, 0.71-1.40) Test for heterogeneity was significant (*P*=0.001)	Supplementation w/ vitD may improve the prognosis of pts w/ advanced prostate cancer, but conflicting study results and imprecise pooled estimates preclude a conclusion. No RCTs assessing the effect of vitD on other cancers were identified for this SR. *Limitations of selected evidence according to Buttigliero et al.:* Adequate sequence generation and allocation concealment unclear; potential bias due to early stopping in 2 trials (Attia 2008, Scher 2010), different chemotherapy

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
NOTE: Only data pertaining to vitD repletion are presented here.	prostate cancer; chemotherapy+vitD vs chemotherapy+placebo (Beer 2007, Attia 2008); chemotherapy+vitD vs chemotherapy+steroid (Scher 2010, n=953); all 3 studies used active vitD (calcitriol or other analog); f/u 11.7-18.3 mos NOTE:Since no mention was made of BL 25-OHD in the SR, primary studies were retrieved; none reported BL 25-OHD or differential effectiveness according to BL levels or any other factor		*Authors' conclusions:* VitD supplementation cannot be recommended at this time for routine clinical practice.	schedules in the 2 arms (Beer 2007), primary endpoint was biochemical response in 2 studies (Attia 2008, Scher 2010). *Other comments on quality of evidence:* Statistical heterogeneity, perhaps due to heterogeneity in tx protocols; largest study (Scher 2010) lacked a true control grp; no analysis of differential effectiveness according to pt factors. *Limitations of the SR:* Factors considered in multivariate HR models NR; no CI reported for Scher 2010 HR.
Cardiovascular Disease				
Witham et al. (2009) University of Dundee, Dundee, Scotland SR and MA to assess the ability of vitD supplementation or ultraviolet radiation to reduce BP *Databases searched:* MEDLINE, Embase, Cochrane database, CINAHL *Search time frame:* 1996 – June 2006 *Funding source:* NR Included RCTs in populations w/	7 RCTs, <545 participants *Population of interest:* Not specified; subgrp of studies in populations w/ HTN presented here *Intervention of interest:* VitD2, vitD3, active (analog) vitD (calcitriol, paricalcitol or doxercalciferol), or ultraviolet B radiation *Outcomes of interest:* Change in office or ambulatory SBP or DBP, other outcomes related to DM or CVD, other adverse events *Study inclusion criteria:* F/u ≥1 wk	*Quality assessment:* Allocation concealment, blinding, BL comparability of grps, description of dropouts, and availability of ITT analysis were categorized as adequate, inadequate, or unable to assess. *Analytic methods:* Fixed models if heterogeneity <50%, as measured by I^2.	*Pooled estimate of difference in change (vitD minus control) (7 RCTs):* SBP: –3.3 mm Hg (CI, –8.2 to 1.7; NS) DBP: –2.3 mm Hg (CI, –4.6 to 0.0; *P*=0.05) Significant heterogeneity >50% was present across the 8 studies in HTN populations, which included 1 study of ultraviolet radiation. *Individual study estimates of difference in change (vitD minus control):* SBP: –13.9 to 5 mm Hg DBP: –9.2 to 0.4 mm Hg *Activated vitD vs vitD2/vitD3:* Effect on SBP was significant only in the subgrp of studies using vitD2/vitD3, but CIs for the 2 subgrp estimates overlapped. No difference in effect	VitD supplementation in individuals w/ HTN living in northern latitudes had a possible small beneficial effect on BP, w/ stronger evidence of an effect on DBP than on SBP. *Quality of included evidence according to Witham et al.:* All studies were RCTs; generally insufficient detail to allow assessment of allocation concealment or ITT analysis; blinding in most studies; no suggestion of publication bias in funnel plot; statistical

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
HTN: Lind 1987, Lind 1988a, Lind 1988b, Lind 1989, Scragg 1995, Pfeifer 2001, Sugden 2008 NOTE: Data and conclusions concerning populations w/ normal BP (SBP ≤140 mm Hg, DBP ≤90 mm Hg, or mean arterial pressure ≤105 mm Hg) at BL and pertaining to ultraviolet radiation as the intervention are not presented here.	*Study exclusion criteria:* NR *Study characteristics:* All conducted in western Europe (latitude >50°N); pts selected for disorders other than HTN in most studies; mean age 48-65 yrs; 19%-100% men; vitD2 (1800 IU/day), vitD3 (800-2000 IU/day), or analog (1 µg/day) except 1 study of ultraviolet B radiation in 1 study; placebo control in most; f/u 5 wks to 6 mos; BL 25-OHD 25-48 nmol/L in 4 studies, NR in 4		on DBP. Data from studies reporting other outcomes are captured for this report in other evidence tables. Witham et al. did not report a pooled estimate for outcomes other than BP. *Authors' conclusions:* There is weak evidence of a small reduction in BP using vitD compounds in pts w/ HTN. Witham et al. cited a study suggestion that a 3 mm Hg reduction in SBP translates to a 10% reduction in CV deaths at population level.	heterogeneity; insufficient reporting and/or too few studies to allow assessment of effect modification by BL 25-OHD or vitD dose; few studies reported a rigorous method for measuring BP. *Other comments on evidence:* Pooled estimate for SBP very imprecise. *Limitation of the review:* Type of assay used NR; no analysis by pt factors.
Abnormal Blood Glucose				
Pittas et al. (2010) *Databases searched:* MEDLINE, Cochrane *Search time frame:* Inception to November 4, 2009 *Funding source:* AHRQ and various other U.S. and Canadian governmental bodies Included RCTs of diabetic pts: Pittas 2007, Sugden 2008, Jorde 2009, von Hurst 2009 NOTE: Observational studies, uncontrolled trials, and RCTs conducted in populations w/o BL diabetes are not presented here.	4 RCTs, 243 participants *Population of interest:* Adults w/ type 2 diabetes *Intervention of interest:* VitD3 or vitD2 *Relevant outcomes of interest:* FPG, HbA1C, incident diabetes, incident HTN, BP *Study inclusion criteria:* RCTs of vitamin D supplementation in adults; cardiometabolic outcomes related to type 2 diabetes *Study exclusion criteria:* Short-term (<1 mo) studies, type 1 diabetes, children, pregnant women, participants w/ conditions that affect vitD metabolism	SR and MA (but MAs were not applicable to this evidence report). Differences in change (vitD minus placebo) were reported. *Quality assessment:* Good-quality studies had clear description of population and setting, unbiased outcome assessments, appropriate statistical analysis, no obvious reporting omissions or errors, and <20% dropouts; fair-quality studies had some deficiencies that are unlikely to cause major bias; poor-quality studies had major deficiencies that may lead to major bias.	*Authors' conclusion:* No clinically significant effect of vitD supplementation at the dosages given.	Authors' conclusions seem reasonable. *Quality of evidence according to Pittas et al.:* All studies judged to be fair; primarily white populations; post hoc analyses. *SR limitations:* Analysis and conclusions did not distinguish between populations w/ and w/o disease at BL, which limits applicability to this report.
George et al. (2012)	6 RCTs, 622 participants	SR and MA (random effects	*Authors' conclusions:* Current evidence is	Authors' conclusions are

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
Databases searched: MEDLINE, Embase, Cochrane, CINAHL *Search time frame:* Inception to March 2011 *Funding source:* No external funding Included RCTs of diabetic pts: Ljunghall 1987, Orwoll 1994, Pittas 2007, Sugden 2008, Jorde 2009, Von Hurst 2009, DeZeeuw 2010, Witham 2010 NOTE: Studies conducted in populations w/o BL diabetes, impaired glucose tolerance, or insulin resistance, are not presented here.	*Population of interest:* Diabetes or impaired glucose control *Intervention of interest:* VitD2, vitD3, calcitriol, alfacalcidiol, paricalcitol, or doxecalciferol *Outcomes of interest:* Fasting glucose, glycated hemoglobin, microvascular complications, macrovascular complications, insulin resistance, C-peptide levels *Study inclusion criteria:* RCTs of vitamin D supplementation w/ or w/o calcium vs placebo or calcium *Study exclusion criteria:* Diabetes other than type 1 or 2, participants already on vitD supplementation, participants w/ end-stage renal failure or primary hyperparathyroidism	models). Pooled estimates expressed as mean difference (FPG, HbA1C) or SMD (insulin resistance, C-peptides), vitD minus placebo. *Quality assessment:* Quality of allocation concealment, potential for selection bias, quality of blinding, ITT analysis, comparability of grps Quality assessment performed independently by two reviewers.	insufficient to recommend vitD supplementation for improving glycemia or insulin resistance in pts w/ diabetes.	reasonable *Quality of evidence according to George et al.:* Unclear or missing ITT analysis in most studies; otherwise, criteria were met; too few studies to allow metaregression analysis of effect modification by BL 25-OHD level or BL glucose/HbA1C. *Limitations of SR:* Loss to f/u or w/drawal rates not specifically identified for studies lacking clear ITT analysis.
Results of Meta-analyses				
George et al. (2012) De Boer 2008, Major 2007, Nilas 1984, Pittas 2007	34,234 individuals w/ abnormal glucose tolerance		*Pooled SMD (George 2012):* HbA1C: –0.32 (CI, –0.57 to –0.07) (no heterogeneity)	
George et al. (2012) Ljunghall 1987, Orwoll 1994, Pittas 2007, Sugden 2008, Jorde 2009, Witham 2010	345 individuals w/ abnormal glucose tolerance		*Pooled SMD (George 2012):* FPG: –0.25 (CI, –0.48 to –0.03) (no heterogeneity)	
George et al. (2012) Ljunghall 1987, Sugden 2008, Jorde 2009, Witham 2010	233 individuals w/ abnormal glucose tolerance		*Pooled SMD (George 2012):* Insulin resistance: 0.03 (CI, –0.18 to 0.23) (no heterogeneity)	
Individual Study Results: Patients with a Diagnosis of Diabetes				
Sugden (2008) UK	n=34 participants (mean age 64 yrs) randomized to vitD (n=17) or placebo (n=17); BL 25-OHD 64	Single dose of 100,000 IU vitD2 or placebo; assessment at 8 wks (equivalent to 1787 IU/day).	*Difference in change (Pittas 2010):* HbA1C (%): 0.06 (CI, –0.28 to 0.40) SBP (mm Hg): –13.9 (–21.2 to –6.6; *P*=0.001)	

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
	nmol/L *Inclusion criteria:* Stable type 2 diabetes		DBP (mm Hg): –4.5 (–9.4 to 0.4) *SMD (George 2012):* FPG: 0.01 (CI, –0.66 to 0.69)	
Jorde and Figenshau (2009) Norway	n=32 participants (mean age 56 yrs, range 21-75) randomized to vitD (n=16) or placebo (n=16); BL 25-OHD 56 nmol/L *Inclusion criteria:* Stable type 2 diabetes, insulin, and metformin tx	40,000 IU vitD3 or placebo wkly for 6 mos (equivalent to 5714 IU/day).	*Difference in change (Pittas 2010):* HbA1C (%): 0 (CI, –0.05 to 0.5) FPG (mmol/L): –0.6 (–2.2 to 1.0) SBP (mm Hg): –4.9 (–13.2 to 3.4) DBP (mm Hg): –1.6 (CI, –7.4 to 4.2) *SMD (George 2012):* FPG: 0.03 (CI, –0.67 to 0.72)	
Witham [Dove] (2010) UK	n=61 participants randomized to two different vitD doses (100,000 IU, n=19; 200,000 IU, n=20) or placebo (n=22); BL 25-OHD 45 nmol/L *Inclusion criteria:* Type 2 diabetes	Participants received single dose of 100,000 or 200,000 IU vitD3 or placebo, assessment at 16 wks (equivalent to 893 or 1786 IU/day).	*SMD (George 2012):* FPG: –0.59 (CI, –1.16 to –0.02)	
deZeeuw (2010) Europe and U.S.	n=272 participants (mean age 64 yrs) randomized to two different paricalcitol doses (1 µg, n=92; 2 µg, n=92) or placebo (n=88); BL 25-OHD 41 *Inclusion criteria:* Type 2 diabetes, albuminuria, tx w/ angiotensin-converting enzyme inhibitor or angiotensin receptor blockers	1 or 2 µg paricalcitol or placebo daily for 24 wks.	NS effect on reduction in the geometric mean urinary albumin/creatinine ratio compared w/ placebo for 1 µg dose (–11% vs placebo; 95% CI, –27 to 8; *P*=0.23) or 2 µg dose (–18% vs placebo; 95% CI, –32 to 0; *P*=0.053).	
Individual Study Results: Individuals with Impaired Glucose Tolerance or Insulin Resistance				
Ljunghall (1987) Sweden	n=65 men (mean age 61-65 yrs) randomized to vitD (n=33) or placebo (n=32); BL 25-OHD 95 nmol/L *Inclusion criteria:*Impaired glucose tolerance; middle-aged men	0.75 µg daily alfacalcidiol or placebo for 3 mos.	*SMD (George 2012):* FPG: –0.17 (–0.66 to 0.32)	
Orwoll (1994) U.S.	n=20 participants w/ type 2 diabetes (mean age 61%); BL 25-	1 µg calcitriol for 2 mos (does not meet inclusion criteria for	*SMD (George 2012):* FPG: 0.08 (CI, –0.54 to 0.70)	

Authors/Study Design	Study Characteristics	Methods	Key Findings/Authors' Conclusions	Comments/Quality/ Limitations
	OHD 35 nmol/L	this evidence report).		
Pittas (2007) (impaired glucose tolerance subgrp) U.S.	n=52 of 92 participants randomized to vitD (n=45) or placebo (n=47); BL 25-OHD 75 nmol/L; mean age 71 yrs *Inclusion criteria:* Impaired FPG	(700 IU vitD3 + 500 mg calcium) or placebo daily for 3 yrs.	*Difference in change (Pittas 2010):* FPG: –0.32 mmol/L (CI, –0.60 to –0.04; *P*=0.042) *SMD (George 2012):* FPG: –0.48 mmol/L (CI, –0.90 to –0.07)	
Von Hurst (2009) New Zealand	n=81 women (mean age 42 yrs, range 23-68) randomized to vitD (n=42) or placebo (n=39); mean BL 25-OHD ~20 nmol/L *Inclusion criteria:* South Asian women; insulin resistance; no diabetes; 25-OHD <50 nmol/L	4000 IU vitD3 or placebo daily for 26 wks	*Difference in change (Pittas 2010)* FPG (mmol/L): 0 Significant improvements in insulin sensitivity (*P*=0.003), insulin resistance (*P*=0.02), and fasting insulin levels (*P*=0.02) compared w/ placebo. No significant difference in FPG (0.1 vs 0.1 nmol/L) in vitD vs placebo grps.	

APPENDIX Vb. Vitamin D Supplementation in Individuals with Chronic Disease: Findings from Randomized Controlled Trials (RCTs)

Key: 25-OHD, 25-hydroxyvitamin D; ANCOVA, analysis of covariance; AN(C)OVA, analysis of (co)variance; BDI, Beck Depression Inventory; BL, baseline; BMI, body mass index; BP, blood pressure; CI, confidence interval; dx, diagnosis; ECLIA, electrochemiluminescence immunoassay; EDSS, Expanded Disability Status Scale; FPG, fasting plasma glucose; f/u, follow-up; g, gram; grp(s), group(s); HbA1C, glycated hemoglobin; hx, history; IL-2, interleukin-2; IOM, Institute of Medicine; ITT, intention-to-treat; IU, international units; µg, microgram; MRI, magnetic resonance imaging; MS, multiple sclerosis; ng, nanogram; nmol, nanomole; NR, not reported; NS, not significant (statistically); NT-proANP, N-terminal propeptide of atrial natriuretic peptide; NT-proBNP, N-terminal propetide of brain natriuretic peptide; OGTT, oral glucose tolerance test; OJ, orange juice; PP, per protocol; pt(s), patient(s); QOL, quality of life; *r*, coefficient correlation; RIA, radioimmunoassay; RRMS, relapsing-remitting MS; TGFB1, transforming growth factor beta-1; tx, treatment; vitD, vitamin D; WHI, Women's Health Initiative; wt, weight

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
Obesity				
Caan et al. (2007) WHI trial *F/u:* 7 yrs *Latitude:* Multicenter, U.S. study *Season:* Yr-round	n=13,189 obese women of 36,184 randomized to vitD (n=18,176; BMI, 28.9±6; total vitD intake, 9±7 µg) or placebo (n=18,106; BMI, 28.8±6; total vitD intake, 9±7 µg); BL 25-OHD NR *Inclusion criteria:* Postmenopausal women; 50-79 yrs of age	Pts received total dose of vitD 400 IU and calcium 1000 mg or placebo/day; double-blinding (participants and staff); study medication discontinued after report of kidney stones, hypercalcemia, dialysis, calcitriol use, or personal supplementation of vitD >1000 IU/day. ITT, linear repeated-measures regression modeling, nominal multinomial logistic regression modeling *Outcome measures:* Body wt	Pts in vitD grp had smaller annual wt gains than those in placebo grp (mean difference –0.13 kg, range –0.21 to –0.05; *P*=0.001). *Mean difference in wt change (kg) according to BL BMI (kg/m^2) (range):* 30 to <35: –0.23 (–0.4 to –0.06) ≥35: –0.17 (–0.38 to 0.04) Pts who were heavier (i.e., higher BMI) had a greater tx effect (*P*=0.04 for interaction). *Adverse effects:* NR	Results suggest that supplementation w/ vitD and calcium reduces the wt gain associated w/ early menopause. *Limitations:* High level of personal vitD supplementation was allowed; therefore, pts in placebo grp may have had same or greater vitD intake as those in tx grp; lack of a vitD-only grp; low tx dose of vitD; method of allocation concealment NR. *Quality:* Fair
Major et al. (2007), Major et al. (2009) Laval University, Ste Foy, Canada *F/u:* 15 wks *Latitude:* 47°N	n=84 overwt or obese women randomized to vitD or placebo *Evaluable participants:* VitD grp (n=30; mean age 43.6±5 yrs) and placebo grp (n=33; mean age 41.6±6.1 yrs); BL 25-OHD NR	Participants received vitD 400 IU and calcium 1200 mg or placebo/day; double-blinding; all participants participated in wt-loss intervention ANOVA, ANCOVA, Pearson	21 participants were excluded from analysis: 11 in vitD grp, 8 in placebo grp, and 2 in NR grp. Intergrp differences in BP, wt loss, FPG, 2-hr postload glycemia, and fasting plasma insulin were NS.	Results suggest that supplementation w/ vitD and calcium in combination w/ a wt-loss intervention have no effect on BP, body wt, and glucose profiles in overwt women. However, subgrp analyses suggest that vitD supplementation promotes wt loss in

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
Season: NR	*Inclusion criteria:* Calcium intake <800 mg/day; no calcium supplements w/in 30 days of study; stable body wt; BMI 27-40 kg/m^2; normal blood pressure; limited exercise; no drugs that could affect wt	correlations, linear regression after adjusting for fat mass and waist circumference, subgrp analyses conducted on participants who had very low calcium intake (≤600 mg/day; vitD grp, n=7; placebo grp, n=6) *Outcome measures:* FPG, OGTT, BP, body wt, BMI	*Very low calcium intake subgrp (vitD; placebo):* Body wt change, kg: –5.8; –1.4 (CI, –5.7 to –1.7; *P*=0.009 for interaction) BMI change, kg/m2: –2.2; –0.5 (CI, –2.2 to –0.7; *P*=0.008 for interaction) These results were adjusted for BL body wt. *Adverse effects:* NR	participants w/ a very low calcium intake. *Limitations:* Method of allocation concealment NR; low dose of vitD; high # dropouts; no ITT analyses; small number of participants in subgrp analyses. *Quality:* Good
Jorde et al. (2008) University of Tromsø, Tromsø; University Hospital of North Norway, Tromsø, Norway *F/u:* 1 yr *Latitude:* 70°N *Season:* Yr-round	n=441 participants randomized to high-dose vitD (n=150; mean age 46 yrs, range 21-70; 57 men, 93 women; 25-OHD 54.5 nmol/L), low-dose vitD (n=142; mean age 48.5 yrs, range 23-70; 51 men, 93 women; 25-OHD 49.1 nmol/L), or placebo (n=149; mean age 48 yrs, range 24-69; 51 men, 98 women; 25-OHD 52.3 nmol/L) *Inclusion criteria:* BMI 28-47 kg/m^2; 21-70 yrs of age; serum calcium ≤2.55 mmol/L; no hx of coronary infarction, angina pectoris, stroke, or renal stones; no use of antidepressants or wt-reducing drugs	All participants received calcium 500 mg/day. Participants also received 40,000 IU vitD3 (high dose); 20,000 vitD3 (low dose); or placebo wkly for 1 yr. Double-blinding. Personal supplementation w/ calcium or vitD was discontinued at study entry. ECLIA (Modular E170) ITT, PP, Mann-Whitney, χ^2 test; Wilcoxon signed ranks test *Outcome measures:* BDI	Dropout rates: High-dose grp 22.7%; low dose grp 25.3%; placebo 24.8% There was significant improvement in BDI scores in both vitD grps, but not placebo grp. Change in BDI subscale 1-13 scores between BL and 1 yr was significantly higher in pooled vitD participants vs placebo grp in PP analysis (*P*<0.05) but not ITT analysis (*P*=0.051). Subgrp analyses revealed that the change in BDI subscale 1-13 score was significant in women in both vitD grps (*P*<0.05). Other variables that were significant for either vitD grp included: age (*P*<0.05); BMI (*P*<0.05); 25-OHD (*P*<0.05); physical activity (*P*<0.01); and BDI subscale score (*P*<0.001). *Adverse effects:* Hypercalcemia in 4 participants in vitD grp and 1 participant in placebo grp;	Results suggest that supplementation w/ vitD and calcium may improve depression in overwt participants w/ hypocalcemia. *Limitations:* Subgrp analyses did not include tx assignment; high rate of dropouts; no vitD-only grp; BDI scores not normally distributed so regression analysis could not be performed; only one measure of depression used; most participants not clinically depressed at BL. *Quality:* Good

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
			hyperparathyroidism in 1 participant in vitD grps and 1 participant in placebo grp. There were no differences in rate of adverse effects between grps.	
Sneve et al. (2008) University of Tromsø, Tromsø; University Hospital of North Norway, Tromsø, Norway *F/u:* 1 yr *Latitude:* 70°N *Season:* Yr-round	n=445 participants randomized to high-dose vitD (n=153; mean age 46.4±11.3 yrs; 57 men, 96 women; wt 101±14.5 kg; BMI 35±4.1 kg/m^2; 25-OHD 54.5±16.7 nmol/L); low-dose vitD (n=143; mean age 47.6±11.9 yrs; 51 men, 92 women; wt 98.6±14.3 kg; BMI 34.4±3.9 kg/m^2; 25-OHD 51.4±18.4 nmol/L); or placebo (n=149; mean age 48.9±11 yrs; 51 men, 98 women; wt 100.6±13.9 kg; BMI 35.1±3.8 kg/m^2; 25-OHD 53.2±15.4 nmol/L) Same population as Jorde 2008 *Inclusion criteria:* See Jorde et al. (2008)	All participants received calcium 500 mg/day. Participants also received 40,000 IU vitD3 (high dose); 20,000 vitD3 (low dose); or placebo wkly for 1 yr. Double-blinding. ITT, *t*-test, Pearson's correlation coefficient, linear regression w/ covariates (age, sex, serum measurements, dietary intakes, smoking, and activity), linear mixed model w/ Toeplitz covariance *Outcome measures:* Body wt	Dropout rates: High-dose grp 24.2%; low-dose grp 25.9%; placebo 24.8% There was no significant change in wt in any grps. Wt changes in relation to BL 25-OHD levels were NS in any grps. *Adverse effects:* See Jorde et al. (2008)	Results suggest that supplementation w/ vitD and calcium has no effect on body wt in overwt participants w/ hypocalcemia. *Limitations:* Subgrp analyses did not include tx assignment; high rate of dropouts; lack of vitD-only grp. *Quality:* Good
Zittermann et al. (2009) Herzzentrum Nordrhein-Westfalen, Bad Oeynhausen, Germany *F/u:* 1 yr *Latitude:* NR *Season:* Yr-round	n=200 participants randomized to vitD or placebo *Evaluable participants:* VitD grp (n=82; mean age 47.4±10.3 yrs; 37.8% men; wt 101.9±16.1 kg; BMI 33.7±4.1 kg/m^2; 25-OHD 30±17.5 nmol/L); placebo grp (n=83; mean age 48.8±10.1 yrs; 27.7% men; wt 96.1±15 kg; BMI 33±9.9 kg/m^2; 25-OHD 30.3±20.1 nmol/L) *Inclusion criteria:* 18-70 yrs of age; BMI >27 kg/m2; no hx of MI, angina pectoris, heart valve disease, cholelithiasis, urolithiasis, insulin-dependent diabetes, or	Participants received 5 vitD3 (3332 IU) drops or placebo drops daily; double-blinding; wt reduction program. RIA (DiaSorin) Data that was not normally distributed was normalized by logarithmic transformation, unpaired *t*-test, ANOVA, ANCOVA. *Outcome measures:* Body wt, BP	18% of participants in vitD grp and 17% of participants in placebo grp w/drew from study. NS time by tx effects on glucose, HbA1C, SBP, DBP, wt, BMI, dietary intakes, energy expenditure, fat mass, or waist circumference. Magnitude of change for these variables was similar between vitD and placebo. *Adverse effects:* NR	Results suggest that supplementation w/ vitD has no effect on glycemic control, body wt, or BP in overwt participants. *Limitations:* No ITT analysis; BP measured only twice in study so small changes in BP could have been missed. *Quality:* Fair

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
	pacemaker; vitD supplementation was not allowed			
Jorde et al. (2010) University Hospital of North Norway, Tromsø, Norway *F/u:* 1 yr *Latitude:* 70°N *Season:* Yr-round	n=438 participants randomized to high-dose vitD (n=150; mean age 46.3±11.3 yrs; 37.3% men; 25-OHD 58.7±21.2 nmol/L); low-dose vitD (n=139; mean age 47.3±11.9 yrs; 36% men; 25-OHD 56.7±21.2 nmol/L); or placebo (n=149; mean age 48.9±11.0 yrs; 34.2% men; 25-OHD 58.8±21 nmol/L) Same population as Jorde et al. (2008) *Inclusion criteria:* See Jorde et al. (2008)	All participants received calcium 500 mg/day. Participants also received 40,000 IU vitD3 (high dose); 20,000 vitD3 (low dose); or placebo wkly for 1 yr. Double-blinding. RIA (DiaSorin) PP, ANOVA, χ^2 test; linear regression w/ covariates (age, sex, smoking status, and serum measurements) *Outcome measures:* OGTT, BP	Dropout rates: High-dose grp 24%; low-dose grp 25.2%; placebo 24.8% Changes in OGTT measurements and diastolic BP by end of study were NS in all grps; low dose grp had significant increase in systolic BP at end of study compared w/ placebo grp (P<0.05). Subgrp analyses of participants w/ low serum 25-OHD (<45 nmol/L) also were NS. Subgrp analyses of participants who were not taking blood pressure drugs revealed the pooled vitD grp had higher change in systolic BP than placebo (P<0.05); there was no difference between grps in those who were taking blood pressure drugs. Subgrp analyses of participants w/ impaired glucose tolerance or impaired fasting glucose at BL revealed a significant increase in plasma glucose 2-hr component of OGTT in vitD pooled grp vs placebo (P<0.05). There were no significant differences w/ other OGTT measures and HbA1C. *Adverse effects:* See Jorde et al. (2008)	Results suggest that supplementation w/ vitD and calcium has no effect on glucose tolerance in overwt participants. There is some evidence that vitD is associated w/ increased BP. *Limitations:* No ITT analysis; several significant differences between PP grp and participants who w/drew from study; high rate of dropouts; lack of vitD-only grp. *Quality:* Fair
Rosenblum et al. (2012) Massachusetts General Hospital, Boston, MA *F/u:* 16 wks	2 RCTs (176 participants) *Regular OJ trial:* n=88 participants randomized to OJ w/ vitD and calcium or unfortified OJ	Regular trial: Participants received regular OJ (placebo grp) or regular OJ fortified w/ calcium 350 mg and vitD3 100 IU (vitD grp) 3x/day for 16 wks. Regular OJ had 110	26.1% of participants in regular OJ trial and 20.5% of participants in Llte OJ trial w/drew; # participants w/drawn from each study arm was NR.	Results suggest that supplementation w/ vitD and calcium has no effect on body wt in overwt participants following a wt reduction program.

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
Latitude: 42°N *Season:* Yr-round	Evaluable participants: VitD grp (n=33; mean age 40±14 yrs; 77% women; wt 85.9±13.1 kg; BMI 30.9±2.7 kg/m^2; 25-OHD 26±10 ng/mL); placebo grp (n=38; mean age 39±14 yrs; 88% women; wt 81.7±10 kg; BMI 29.8±2.8 kg/m^2; 25-OHD 27±13 ng/mL) *Lite OJ trial:* n=88 participants randomized to lite OJ w/ vitD and calcium or unfortified OJ Evaluable participants: VitD grp (n=42; mean age 39±13 yrs; 95% women; wt 78.2±10.9 kg; BMI 30±2.7 kg/m^2; 25-OHD 31±12 ng/mL); placebo grp (n=41; mean age 43±11 yrs; 95% women; wt 79.9±9.01 kg; BMI 30±2.6 kg/m^2; 25-OHD 33±13 ng/mL) *Inclusion criteria:* 18-65 yrs of age; BMI 25-35 kg/m^2; stable wt for ≥3 mos before study; 25-OHD >10 ng/mL; <2 servings dairy product/day; no hx of diabetes, polycystic ovary syndrome, parathyroid disease, sarcoidosis, substance abuse, or eating disorder; no drugs that cause wt change in ≤6 mos of study	kcal/serving. Lite trial: Participants received lite OJ (placebo grp) or lite OJ fortified w/ calcium 350 mg and vitD3 100 IU (vitD grp) 3x/day for 16 wks. Lite OJ had 50 kcal/serving. All participants received diet and exercise counseling. Participants were not allowed to take multivitamins or calcium supplements >2×/wk. Double-blinding (participants and investigators). ECLIA (Elecsys 170 Modular) ITT, PP, *t*-test, ANCOVA, ANOVA *Outcome measure:* Body wt	In both trials, changes in body wt in each grp were NS and differences between grps were NS. Changes in body wt were NS after adjusting for BL total abdominal fat. When data from both studies were combined, changes in body wt remained NS. *Adverse effects:* NR	*Limitations:* High rate of dropouts; very low vitD dose compared w/ other studies; multivitamin and calcium supplements were allowed; no vitD-only grp. *Quality:* Good
Diabetes, Impaired Glucose Tolerance, or Insulin Resistance				
Mitri et al. (2011) Tufts Medical Center, Boston, MA *F/u:* 16 wks *Latitude:* 42°N *Season:* Yr-round	n=92 pts at high risk of diabetes randomized to vitD and calcium grp (n=23; mean age 57±2 yrs; 11 men, 12 women; 25-OHD 22.4±1.6 ng/mL), vitD grp (n=23; mean age 57±2 yrs; 11 men, 12 women; 25-OHD 26.5±1.6 ng/mL), vitC grp (n=22; mean age 57±2 yrs; 12	VitD and calcium grp: VitD3 2000 IU and calcium 800 mg daily VitD grp: VitD3 2000 IU and calcium placebo daily Calcium grp: Calcium 800 mg and vitD placebo daily Placebo grp: Calcium placebo and vitD placebo daily	1 participant in vitD grp, 1 participant in calcium grp, and 2 participants in placebo grp w/drew from study. *Adjusted change (P for tx):* VitD vs no vitD: HbA1C, 0.08% vs 0.03% (*P*=0.024) after	Results suggest that supplementation w/ vitD has no effect on glycemic control in participants w/ impaired glucose tolerance or early diabetes. *Limitations:* Small # participants in each study grp; study was not powered for the glycemic outcomes;

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
	men, 10 women; 25-OHD 25±1.8 ng/mL), or placebo grp (n=24; mean age 59±2 yrs; 11 men, 13 women; BL 25-OHD 24.2 ng/mL [60.5 nmol/L]) *Inclusion criteria:* Ambulatory, ≥40 yrs of age; BMI ≥25 kg/m^2; glucose intolerance (FPG ≥100 mg/dL, or 2-hr glucose ≥140 mg/dL after 75 g oral dextrose, or HbA1C ≥5.8%); no wt change >4 kg in previous 6 mos; no supplementation w/ vitD or calcium ≤8 wks before study; no hx of hyperparathyroidism, hypercalcemia, nephrolithiasis, or kidney disease; no conditions that may effect vitD or calcium metabolism	Double-blinding, including lab measurements. LC-MS ITT, ANOVA, χ^2 test, linear models (adjusted for age, BMI, race, season of study entry) *Outcome measures:* HbA1C, FPG, 2-hr plasma glucose	elimination of 2 outliers; no effect on FPG or 2-hr plasma glucose VitD+calcium vs placebo: HbA1C, 0.05% vs 0.18% (*P*=0.036) VitD vs placebo: FPG. 24 mmol/L vs 8.4 mmol/L (*P*-0.051) *Adverse effects:* There was no difference in the incidence of adverse effects between grps. There was no nephrolithiasis or hypercalcemia reported.	no adjustment for multiple testing. *Quality:* Fair
Nikooyeh et al. (2011) Shahid Beheshti University of Medical Sciences, Tehran, Iran *F/u:* 12 wks *Latitude:* 37°N *Season:* Fall and winter	n=90 participants (35 men, 55 women) randomized to vitD/low calcium grp (n=30; mean age 51.4±5.4 yrs), vitD/high calcium grp (n=30; mean age 49.9±6.2 yrs), or placebo (n=30; mean age 50.8±6.6 yrs) *BL 25-OHD:* <27.5 nmol/L (38.9%), 27.5 to <50 nmol/L (34.4%), ≥50 nmol/L (26.7%) *Inclusion criteria:* Type 2 diabetes; 30-60 yrs of age; fasting plasma glucose ≥126 mg/dL; no vitD, calcium, or omega-3 supplementation ≤3 mos prior to study; no use of drugs or hx of conditions that effect vitD metabolism; no use of insulin	Participants received plain yogurt drink (placebo grp), yogurt drink w/ vitD3 500 IU and calcium 150 mg (vitD/low calcium grp), or yogurt drink w/ vitD3 500 IU and calcium 250 mg (vitD/high calcium grp) twice daily for 12 wks; all participants participated in wt maintenance diabetic diet; double-blinding. HPLC ANOVA, t-test, χ^2 test, Pearson's correlation, Spearman's correlation *Outcome measures:* Body wt, BP, HbA1C, fasting serum insulin, FPG	Differences in change in FPG, fasting serum insulin, insulin resistance, HbA1C, wt, BMI, waist circumference, and waist-to-hip ratio were small but statistically significant and favored vitD or vitD+calcium. Change in BP did not differ between grps. There was a significant inverse relationship between changes in 25-OHD and changes in wt (*r*=–0.331, *P*=0.001), FPG (*r*=–0.208, *P*=0.049), serum insulin (*r*=–0.308, *P*=0.003), and HbA1C (*r*=–0.215, *P*=0.042). *Adverse effects:* NR	Results suggest that supplementation w/ vitD or vitD+calcium has small beneficial effects on wt and glycemic control but no effect on BP in pts w/ type 2 diabetes. *Limitations:* Method of allocation concealment NR; vitD+calcium grp was substantially more likely to be vitD deficient (trend towad global significance); no correction for multiple testing; no statistical assessment of differences in change. *Quality:* Poor
Eftekhari et al. (2011)	n=70 women w/ gestational	Participants received calcitriol 0.5	There were no significant	Results suggest that supplementation

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
Shiraz University of Medical Science, Shiraz, Iran *F/u:* 12 wks *Latitude:* 30°N *Season:* Summer and fall	diabetes randomized to vitD (n=35; mean age 53.8±8.9 yrs) or placebo (n=35; mean age 52.4±7.8 yrs); BL 25-OHD NR *Inclusion criteria:* Type 2 diabetes; 30-75 yrs of age; oral hypoglycemic drugs; well-controlled FPG; serum calcium <10.5 mg/dL; no hx of kidney stones, hypercalcemia, intestinal malabsorption disease, or diseases affecting vitD metabolism; no insulin or vitD or calcium supplements	µg or placebo daily; double-blinding. RIA Independent t-test, paired t-test, linear model repeated measures *Outcome measures:* FPG; fasting insulin, HbA1C	differences in the mean FPG, fasting insulin, or HbA1C between grps at any time point of study. Repeated measurements analyses revealed significant increases in FPG in placebo grp (*P*=0.038) but not vitD grp (*P*=0.712; difference between grps *P*<0.05). Fasting insulin and HbA1C significantly increased in both grps (all analyses *P*≤0.01). *Adverse effects:* Participants in vitD grp had increased plasma phosphorus resulting from calcitriol use	w/ vitD prevents the increase over time in fasting plasma glucose typically seen in participants w/ diabetes. *Limitations:* Randomization method NR. *Quality:* Good
Mozaffari-Khosravi et al. (2012) Yazd Diabetes Research Center, Yazd; Shahid Sadoughi University of Medical Sciences, Yazd, Iran *F/u:* 3 mos *Latitude:* 32°N *Season:* NR	n=45 participants randomized to vitD (n=24; mean age 30.7±6.2 yrs; HbA1C, 5.48±0.69%; 25-OHD <35 nmol/L, 79.2%) or control (n=21; mean age 29.5±4 yrs; HbA1C, 5.2±0.73%; 25-OHD <35 nmol/L, 76.2%) *Inclusion criteria:* First time gestational diabetes; no hx of thyroid, renal, or hepatic disease; no malabsorption	Participants in vitD grp received 1 injection of vitD3 300,000 IU immediately after delivery; participants in control grp did not receive intervention. Immunoassay (NycoCard) Paired t-test, Student's t-test, Kolmogorov-Smirnov test, Wilcoxon test, Mann-Whitney, Fisher's exact test *Outcome measures:* OGTT, HbA1C, FPG	Changes in FPG, OGTT, and HbA1C were similar and change differences NS. Insulin sensitivity substantially dropped in control grp but remained stable in vitD grp (*P*=0.002). Insulin resistance stayed high in control grp but declined in vitD grp (homeostasis model assessment, *P*=0.004; C-peptide *P*=0.05). *Adverse effects:* No incidence of hypercalcemia; infants had normal growth and well-being	Results suggest that a single injection of vitD following delivery had no effect on glycemia but improved insulin resistance. *Limitations:* Small # participants in each grp; no placebo grp. *Quality:* Fair
Multiple Sclerosis				
Mahon et al. (2003) Pennsylvania State University, University Park, PA; Helen Hayes Hospital, West Haverstraw, NY	n=39 pts w/ dx of MS (men and women; mean 25-OHD 42.5 nmol/L) randomized to vitD (1000 IU/day) + calcium (n=17) or calcium+placebo (n=22)	Double-blinding 2-factor repeated-measures ANOVA; correction for multiple testing for tests of differences in	At 6 mos, TGFB1 levels were substantially higher in vitD+calcium grp and unchanged in placebo grp.	Results suggest that vitD had a partial, beneficial effect on disease markers in individuals w/ MS who were on avg at risk of vitD deficiency according to IOM recommendations for healthy

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
F/u: 6 mos *Latitude:* 41°N *Season:* NR NOTE: This study represents interim results from a larger 2-yr study; the complete study was not identified in the published literature.	48% study grp had 25-OHD levels <50 nmol/L	means. *Outcome measures:* Changes in serum levels of 2 anti-inflammatory cytokines (TGFB1, IL-2) and 4 inflammatory cytokines	IL-2 levels diminished to a greater extent in vitD+calcium grp than in placebo grp, but significance of between-grp differences was NR. Changes and between-grp differences in inflammatory cytokines were contradictory and NS. Mean 25-OHD level at 6 mos in the vitD grp was 70 nmol/L.	individuals. *Limitations:* Interim analysis not followed by publication of full trial; surrogate outcome measures. *Quality:* Fair
Burton et al. (2010); Kimball et al. (2011) St. Michael's Hospital, Toronto, Canada *F/u:* 52 wks *Latitude:* 44°N *Season:* Yr-round	n=49 participants matched and then randomized to vitD (n=25; mean age 41.1±7.4 yrs; 4 men, 21 women; 25-OHD 73±26 nmol/L) or control (n=24; mean age 39.9±8.6 yrs; 5 men, 19 women; 25-OHD 83±27 nmol/L) Participants matched for age, disease duration, EDSS, and disease-modifying drug use, then participants randomly assigned to vitD or control grps. *Inclusion criteria:* Clinically-confirmed MS; 18-55 yrs of age; vitD intake ≤4000 IU/day; 25-OHD ≤150 nmol/L; no relapse ≤60 days of study; no steroid use in ≤30 days or chemotherapy ≤12 mos of study; no lymphoma, granulomatous disease, cardiac arrhythmia, kidney disease, or altered calcium metabolism	Participants in vitD grp received vitD3 and calcium 1200 mg/day; calcium was initiated 2 wks before initiation of vitD; vitD dose increased stepwise from 4000 IU/day to a maximum of 40,000 IU/day then decreased to 0 for final 4 wks of study (avg 14,000 IU/day); calcium supplementation ceased in final 4 wks of study. Control participants were allowed to supplement w/ ≤4000 nmol/L vitD and/or calcium (dose NR); all participants maintained use of MS disease-modifying drugs. Serum 25-OHD measured by RIA (DiaSorin). ITT, Sign ranks test, McNemar test, Wilcoxon rank sum test; correction for multiple testing in assessment of response to antigens *Outcome measures:* MS relapse rate, disability, proliferative response (blood tests) to MS-	2 participants in each grp w/drew from study. *Clinical responses:* Annual relapse rate was lower in vitD grp (0.26; CI, –0.06 to 0.53) than control grp (0.45; CI, 0.19-0.72), but the difference between grps was NS (*P*=0.09). Proportion of participants completing trial w/ increased EDSS was 0.08 for vitD grp and 0.375 for control grp (*P*=0.019). *Peripheral blood mononuclear cell proliferative responses:* Reduction in response to 7 of 17 antigens was significantly greater in vitD+calcium grp than in control grp (*P*≤0.001). Differences w/ respect to the other 10 antigens were NS. Between-grp differences were significant overall and for 3 of 5 subsets of antigens. *Adverse effects:* There were no adverse effects related to vitD	Results suggest that supplementation w/ vitD and calcium had a beneficial effect on MS disease activity in individuals who were vitD-replete at the beginning of the study. *Limitations:* Not blinded; primary focus of study was safety of high doses of vitD; study not powered to detect significant differences in clinical outcomes; participant matching required limited enrollment; tx grp monitored more frequently than control grp; control grp allowed to take vitD and calcium supplements. *Quality:* Fair

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
		associated antigens	supplementation; participants had normal renal and hepatic function	
Mosayebi et al. (2011) Arak University of Medical Sciences, Arak, Iran *F/u:* 7 mos *Latitude:* 34°N *Season:* Yr-round	n=62 participants randomized to vitD (n=28) or placebo (n=34) Evaluable participants: VitD grp (n=26; mean age 37±9 yrs; 9 men, 17 women; 25-OHD ≈25 nmol/L); placebo grp (n=33; mean age 35±9 yrs; 8 men, 25 women; 25-OHD ≈25 nmol/L) *Inclusion criteria:* Iranian; 18-60 yrs of age; MS; ≥1 relapse in 12 mos before study; >3 lesions on spinal and/or brain MRI; EDSS ≤3.5; no clinically isolated syndrome or progressive MS; no vitD supplementation; no conditions predisposing to hypercalcemia; no hx nephrolithiasis or renal insufficiency	Participants received intramuscular injection of vitD3 300,000 IU or placebo every mo for 6 mos; all participants received interferon B-1a; double-blinding (participant, neurologist, physician, and radiologist) Enzyme immunoassay (Immunodiagnostic Systems Inc.) Mann-Whitney, Wilcoxon *Outcome measures:* EDSS, MRI	2 participants in vitD grp and 1 participant in placebo grp w/drew from study and were not included in analyses. NS changes in EDSS and # lesions w/in or between grps (all analyses $P>0.05$). *Adverse effects:* NR	Results suggest that supplementation w/ vitD has no effect on disability and # lesions of participants w/ MS. *Limitations:* No ITT analyses; small # participants in each grp; method of allocation concealment NR; randomization method NR; possibly underpowered. *Quality:* Fair
Soilu-Hänninen et al. (2012) University Hospital of Turku, Turku, Finland *F/u:* 1 yr *Latitude:*60°N *Season:* All-year	n=66 pts randomized to vitD3 or placebo (25 men, 41 women; median age 39 yrs vitD3, 35 yrs placebo, range 22-53), BMI 24; EDSS score 2.0 vitD, 1.5 placebo; mean BL 25-OHD NR *Inclusion criteria:* Age 18-55 yrs, RRMS; interferon-1b for ≥1 mo; EDSS ≤5.0; use of contraceptives *Exclusion criteria:* Serum calcium >2.6 mmol/L, serum 25-OHD >85 nmol/L; primary hyperparathyroidism or hypoparathyroidism; kidney stones; pregnancy; substance	Weekly vitD3 (20,000 IU; equivalent to 2857 IU/day) or placebo; double-blinding DiaSorin RIA Sample size selected for 80% power to detect 30% difference in proportion of pts w/ 25-OHD ≥85 nmol/L; logistic and linear regression; ANCOVA to analyze time effects adjusted for BL and center values; correlations *Primary outcome measures:* T2 burden of disease, proportion of pts w/ serum 25-OHD ≥85 nmol/L	*% pts w/ serum 25-OHD >85 nmol/L (vitD, placebo):* 6 mos: 6%, 3% ($P<0.001$) 12 mos: 84%, 3% ($P<0.001$) Increase in T2 burden of disease was greater in placebo grp (287 mm^3) than in vitD grp (83 mm^3) (NS). Fewergadolinium-enhancing lesions on T1 MRI at 12 mos in vitD grp ($P=0.004$). Most other differences in MRI changes were NS. Improvement in EDSS score and walking test times favored vitD grp but were NS. No difference in	Although 20,000 IU vitD3/wk was effective in raising serum 25-OHD levels and 1 of several MRI findings, no effect on disease-related outcomes was observed. *Limitations:* Underpowered for functional and other pt-important outcomes. Funded by commericial pharmaceutical firms, but sponsors did not contribute to design, execution, or interpretation of study. *Quality:* Good (for intermediate outcome of serum 25-OHD)

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
	abuse; immunomodulatory tx other than interferon-1b; serious systemic disease	or intact parathyroid hormone ≤20 ng/L, adverse events *Secondary outcome measures:* Change in EDSS, relapse rate, time to first relapse, change in walking tests, MRI changes	relapse rates at 12 mos. *Adverse events:* No hypercalcemia in vitD grp; no between-grp differences in other laboratory outcomes; diahrrea in 5 vitD pts and 2 placebo pts	
Cardiovascular Disease				
Schleithoff et al. (2006) University of Bonn, Bonn, Germany *F/u:* 9 mos tx; 15 mos f/u *Latitude:* 51°N *Season:* All yr	n=93 evaluable pts of 123 pts w/ congestive heart failure VitD grp (n=61): 85% men; mean age 57 yrs (range 53-63); mean BL serum 25-OHD 36 nmol/L Placebo grp (n=62): 81% men; mean age 54 yrs (range 50-62); mean BL serum 25-OHD 38 nmol/L *Inclusion criteria:* New Hork Heart Association Class ≥II *Exclusion criteria:* Hypercalcemia, serum creatinine <2 mg/dL, nephrolithiasis, sarcoidosis, biventricular pacemaker, acute heart insufficiency, use of vitD or calcium supplements	Pts were assigned w/ double blinding to 2000 IU/day vitD3+calcium or placebo+calcium. RIA (DiaSorin) ANOVA for differences in change from BL, paired t test for time effects, Kaplan-Meier analysis of survival *Primary outcome measures:* Survival, biochemical variables *Secondary outcome measures:* Hemodynamic variables	*W/drawal before 9 mos:* n=30 (19 in vitD grp and 11 in placebo grp). Of the 30, 5 were due to noncompliance and 25 due to worsening health; 25 had significantly higher BL levels of NT-proBNP and NT-proANP and slightly lower BL serum 25-OHD w/ a trend toward significance. Differences in change at 9 mos from BL were NS and generally slight for cardiovascular biochemical and hemodynamic variables. 15-mo survival was was very similar. 25-OHD levels at 9 mos exceeded 50 nmol/L in vitD grp and almost reached that level in placebo grp. Dietary intake of vitD and calcium and medication use did not change significantly in either grp during study period. *Adverse effects:* NR	VitD3+calcium, compared w/ calcium alone, did not improve outcomes in pts w/ congestive heart failure and mean vitD deficiency. *Limitations:* Method of allocation concealment NR; 24% w/drawal rate, unbalanced between grps; given the reasons for w/drawal, results may not be generalizable to stable congestive heart failure; no ITT analysis. *Quality:* Poor
Witham et al. (2010a) University of Dundee, Dundee, UK *F/u:* 20 wks	n=105 participants randomized to vitD (n=53; mean age 78.8±5.6 yrs; 34 men, 19 women; 25-OHD 20.5±8.9 nmol/L) or placebo	Participants received vitD2 100,000 IU or placebo at BL and at 10 wks; double-blinding.	3 pts in vitD grp and 2 pts in placebo grp w/drew from study. There were no significant changes	Results suggest that supplementation w/ vitD has no effect on quality of life in participants w/ chronic heart failure.

Authors/Study Design	Study Population	Protocol	Results	Conclusions/Comments/Limitations
Latitude: 56°N Season: NR	(n=52; mean age 80.6±5.7 yrs; 35 men, 17 women; 25-OHD 23.7±10 nmol/L) *Inclusion criteria:* Chronic heart failure; ≥70 yrs of age; left ventricular systolic dysfunction; New York Heart Association Class II or III; vitD <50 nmol/L; no osteomalacia, vitD supplementation, liver disease, or malignancy	RIA Student t-test, Mann-Whitney test, Pearson χ2 test *Outcome measures:* Minnesota Living With Heart Failure questionnaire, Functional Limitations Profile	in the Functional Limitations Profile w/in or between grps (all analyses *P*≥0.13). No difference in improvement in 6-min walk time. VitD grp had a greater increase in the Minnesota Living With Heart Failure questionnaire score at 20 wks compared w/ placebo (difference between grps = 5.3; CI, 0.5-10.2; *P*=0.03); BL scores were 23.6 and 24.7. *Adverse effects:* Mild hypercalcemia in 2 participants in vitD grp and 1 in placebo grp; increased serum creatinine in 5 participants in vitD grp and 1 in placebo grp	*Limitations:* Ergocalciferol has shorter half-life than vitD3, so long spacing between dosing could have prevented steady state levels of vitD from being attained; QOL measures were secondary outcomes; therefore, study may not have had power to detect differences between grps. *Quality:* Good

APPENDIX VI. Cost-Effectiveness Studies and Cost Analyses

Key: C/E, cost-effectiveness; CI, confidence interval; C/U, cost-utility; f/u, follow-up; grp(s), group(s); ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; IU, international unit; LTC, long-term care; MA, meta-analysis; N/A, not applicable; ng, nanogram; NH, nursing home; NR, not reported; pt(s), patient(s); QALY, quality-adjusted life-year; QOL, quality of life; RCT, randomized controlled trial; rehab, rehabilitation; RR, relative risk; tx, treatment; tx'd, treated; VA, Veterans Administration; vitD(K), vitamin D(K)

Authors/Study Design	Population/Intervention/ Comparators/Outcomes	Data Sources/Methods	Results/Authors' Conclusions	Comments/Limitations
Gajic-Veljanoski et al. (2012) University of Toronto, Toronto, Canada C/E study of vitD+calcium and vitD+calcium+vitK (probabilistic decision analytic model) *Perspective:* Payer *Time horizon:* Lifetime or age 100 yrs *Funding source:* No external funding	50-yr-old postmenopausal women w/o osteoporosis VitD3 (800 IU/day) + calcium (1200 mg/day) VitD3+calcium+vitK_2 VitD3+calcium+Vit K_1 VitK_2alone No supplementation Hip, clinical vertebral, morphometric vertebral, or wrist fracture	*Assumptions:* Duration of QOL and cost impact varied by fracture. Woman would take alendronate for 5 yrs after first clinical fracture. *Fracture risk:* Swedish Malmö registry (age- and site-specific) and published MA (for successive fractures). *Mortality risk:* Canadian life tables; increased for 1 yr after hip fracture. *Effectiveness:* VitD: Authors' MA of 3 RCTs† (hip, RR=0.68; vertebral, RR=0.87; wrist, RR=0.69) VitK_2: Published MA and single study in Japanese pts VitK_1: Single RCT in postmenopausal Canadian women *Utility wts:* Published literature *Costs:* All direct medical costs for tx'd fracture, including LTC. Cost of alendronate, vitD3+calcium (CAD 89.90/yr [USD 85.69]; no dispensing costs), and vitK. *Discounting:* 3% for costs and life-yrs *Base yr, inflation adjustment:* 2009 USD, NR	*VitD+calcium*: Cost-saving (–$4196 to –$4283 per woman) over a liftetime. Because of dominance over no supplementation, vitD+calcium became relavant comparison for vitK tx's. *VitD+calcium+vitK:* $9557-$12,896/QALY *VitK_2 alone:* More expensive and less effective than vitD+calcium+vitK NOTE: ICERs were the result of computer simulation w/ repeated sampling; thus, estimates varied slightly for different sets of calculations for different vitK interventions. *Sensitivity analyses:* Varied all input parameters and several base case assumptions. Most sentivie to assumptions regarding effectiveness and costs of vitK. *Authors' conclusions:* No overall conclusion concerning vitD supplementation since vit K supplementation was the focus.	VitD supplementation in 50-yr-old postmenopausal women may reduce direct medical costs associated w/ fracture tx. *Limitations:* RCTs serving as source of vitD effectiveness estimate did not exactly match vitD dose assumptions, included some pts w/ previous vertebral fracture, and were conducted in women generally substantially older than in the base case of this analysis; rationale for selection of vitD trials and MA methods NR; lower RR estimate than calculated by Chung et al. (2011). Authors reported they had no conflicts of interest.
Lilliu et al. (2003) Cost data from 7 European countries (Belgium, France,	Institutionalized women Supplementation w/ vitD3 (800 IU/day) + calcium	*Fracture risk:* Prevalence in the study grp of the effectiveness estimate source (Chapuy et al., 1992). *Effectiveness:* RCT w/ placebo control and ITT	Cost-saving for all countries: €79,000-€711,000 (USD 87,137-USD 784,233)/1000 women. Greatest cost savings for the country	VitD3+calcium supplementation appears to be at best cost-saving and at worst, reasonably cost-effective compared w/ no tx, for prevention of

Authors/Study Design	Population/Intervention/ Comparators/Outcomes	Data Sources/Methods	Results/Authors' Conclusions	Comments/Limitations
Germany, Netherlands, Spain, Sweden, UK) C/E and cost analysis *Perspective:* Mixed *Time horizon:* ≤1 yr postfracture (costs)	(1200 mg/day) No supplementation Hip fracture	analysis (Chapuy et al., 1992); 25% fewer cases (RR 0.75)* *Costs:* Published data for each country. (1) Supplements (€0.29/day-€0.54/day); (2) tx of hip fracture. Cost components varied by country (medical only vs societal, incremental vs total, 6 mos to 1 yr, initial costs only vs midterm rehab also, derived from previously noninstitutionalized population in 1 country). Estimates corresponded to 880 IU/day vitD and/or 1000 mg/day calcium in some countries. Cost of delivering supplements considered negligible. Long-term institutionalization not included as a cost consequence. *Discounting:* N/A *Base yr, inflation adjustment:* NR (2003 assumed), N/A	(UK) for which cost estimates derived from noninstitutionalized population. *Sensitivity analyses:* For worst case scenario (20% increase in # fractures), results suggested that supplementation either remained cost-saving (€123,000-€174,000/1000 women [USD 135,669-USD 191,922/1000 women]) or was reasonably cost-effective (€64,000-€134,000/1000 women [USD 70,592-USD 147,802/1000 women]) in additional costs. Highly cost-saving for all countries under best-case scenario (20% fewer fractures). Daily supplementation price for equal costs in supplementation and placebo grps, €0.64-€1.45 (USD 0.64-USD 1.60). Currency conversions based on rates as of April 25, 2003. *Authors' conclusions:* Analysis probably underestimates C/E since supplementation has been shown to also prevent nonvertebral fractures other than hip.	hip fracture in institutionalized women. *Limitations:* Single older trial as source of effectiveness estimate; slight error in RR calculation for supplementation effectiveness; cost data from multiple non-trial sources; variation across countries in components included in cost estimates (but Lilliu et al. note that the impact of differences is minimimal since there is not a great difference between incremental and total costs for tx of hip fracture and costs are driven by initial hospitalization); no sensitivity analysis based on variation of costs; I concomitant use of osteoporosis medication in trial providing effectiveness estimate.
Singh et al. (2004) Canada C/E and C/U analysis (decision analytic modeling using hypothetical cohort) *Perspective:* Described as "societal" but only direct medical costs were considered;	Elderly NH residents Hip protectors vs standard care No tx or vitD3+calcium supplementation (800 IU/day vitD, 1200 mg/day calcium) Hip fractures averted, QALYs gained	*BL incidence:* 43/1000 persons/yr, based on chart review of a local NH facility. *Effectiveness estimate:* Obtained from a Cochrane Review of hip protectors (RR=0.37) and from Chapuy et al. (1992) for supplementation (RR=0.73*). *Utility values (for QALY estimates):* Published study of EuroQol scores for pts aged 75-84 yrs w/ and w/o hip fracture for 1st and 2nd yrs postfracture; subsequent yrs assumed to be equivalent to 2nd yr. Probability of death for 1st yr, 10%; for subsequent yrs, based on Canadian Life Table data for NH home	*Cost savings/hip fracture averted:* Hip proctector vs no tx: CAD 10,713 (USD 7820) Hip protector vs supplementation: CAD –10,198 (USD –7445) *Cost savings/QALY gained (women; men):* Hip protector vs no tx: CAD 16,204 (USD 11,829); CAD 18,272 (USD 13,339) Hip protector vs supplementation: CAD 15,426 (USD 11,261); CAD 17,394 (USD 12,698)	VitD+calcium supplementation may be a more expensive option than hip protectors for elderly NH residents. *Limitations:* Single, older trials as source of effectiveness estimate; effectiveness estimate may not apply to men; I concomitant use of osteoporosis medication in trial providing effectiveness estimate.

Authors/Study Design	Population/Intervention/ Comparators/Outcomes	Data Sources/Methods	Results/Authors' Conclusions	Comments/Limitations
equivalent to payer perspective *Time horizon:* 1 yr postfracture (costs), lifetime (QALYs gained)		residents w/o fracture. 0.63, no fracture; 0.43, 1 yr postfracture; 0.53, 2nd or subsequent yr postfracture. *Costs (1 yr):* Cost of fracture tx included only immediate hospitalization in the base case and was estimated by finance dept of local hospital associated w/ NH. Cost of hip protector (CAD 150, USD 110) and supplements (CAD 56, USD 41) obtained from local retail suppliers; cost of side effects excluded (evidence suggests they are negligible). *Discounting:* N/A for costs; 3% for QALYs. *Base yr/inflation rate:* 2001, N/A	*2-way and 1-way sensitivity analysis, hip protector vs supplementation:* Limits of 95% CI of effectiveness estimate for hip proctectors, 33% increase and decrease in costs, and addition of nursing aide for putting on protector. Analyses yielded C/E ratios of $299-$18,727/fracture averted and $403-$28,326/QALY, when cost of nursing aid was considered and/or upper limit of effectiveness was assumed; otherwise, cost savings were maintained. *Probabilitic sensitivity analysis (computer simulation), hip protector vs supplementation:* 95% probability that cost/fracture averted is <CAD 20,000 (USD 14,600); 96% probability of cost savings if no nursing aide time is required and cost of hip protector is <CAD 150 (USD 110). Similar findings for QALYs gained as the outcome. *Authors' conclusion:* Hip protectors appear to be a cost-effective tx option.	
Bailey et al. (2012) 6 VA Medical Centers Cross-sectional analysis of costs vs vitD status and monitoring (retrospective chart review) *Perspective:* VA Medical Centers	15,340 pts(mean age 67 yrs; mean BMI 29; 93% men; 88% white) seen at 6 VA Medical Centers in WV, KY, and TN F/u vitD testing vs no f/u Total inpt and outpt costs	<20 ng/mL was considered vitD insufficient. % pts w/ ≥ f/u test ranged from approx 48% to 69%. *Discounting:* N/A *Base yr/inflation rate:* NR, N/A	*Total outpt costs (no f/u test, 1 f/u test; ≥2 f/u tests, vitD deficient, nondeficient):* Approx $76,000; $83,000; $10,200; $10,000, $8000 *Total inpt costs (no f/u test, 1 f/u test; ≥2 f/u tests, vitD deficient, nondeficient):* Approx $11,500; $7500; $6250; $11,000, $7000 Latitude, season of vitD draw, and vitD status, and monitoring were statistically significant explanations of cost variation, but considerable residual variation was	VitD insufficiency may be associated w/ increased healthcare costs. Assuming routine vitD serum testing, monitoring may lead to reduced costs. *Limitations:* Unclear method of statistical testing for cost differences; no assessment of cost implications of routine testing vs no testing; no data on pts' initial test results, disease prevalence and severity, or prescribed supplementation regimens; results may not be

Authors/Study Design	Population/Intervention/ Comparators/Outcomes	Data Sources/Methods	Results/Authors' Conclusions	Comments/Limitations
Time frame: 1 yr following initial blood draw			attributed to site. *Authors' conclusions:* Testing serum vitD once or twice yrly until stable and appropriate levels are documented is appropriate.	generalizable to women or to individuals who are not overwt.

*Intention-to-treat data reported by Chapuy et al. (1992) for 18 months of treatment: 80 hip fractures in 1387 women taking supplements; 110 hip fractures in 1403 women taking placebo; this translates to a relative risk of 0.74. Intention-to-treat data reported by Chapuy et al. (1994) for 3 years of treatment: 138 hip fractures in 1176 women and 184 hip fractures in 1127 women; this translates to a relative risk of 0.72.

†Dawson-Hughes et al. (1997) (men and women age ≥ 65 years), Grant et al. (2005) (men and women age ≥ 70 years), and Jackon et al. (2006) (postmenopausal women age 50 to 70 years, mean 62). All 3 trials included in first Agency for Healthcare Research and Quality report on vitamin D and calcium (Cranney et al., 2007). Vitamin D3 (400-800 IU/day) plus calcium (1000 mg/day).

APPENDIX VII. Excluded Studies

The following studies were excluded for reasons other than the prespecified inclusion/exclusion criteria:

Avenell A, Maclennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD Trial). *J Clin Endocrinol Metab*. 2012;97(2):614-622.

> A randomized controlled trial (RCT) evaluating the effect of vitamin D and calcium supplementation on mortality, vascular disease, and cancer in individuals with a previous low-trauma fracture. This study did not evaluate either the effect of supplementation on disease prevention in a general population (participants were selected because of evidence of poor skeletal health) or the effect on disease-related outcomes in a population defined by disease (skeletal outcomes were not assessed).

Church J, Goodall S, Norman R, Haas M. An economic evaluation of community and residential aged care falls prevention strategies in NSW. *N S W Public Health Bull*. 2011;22(3-4):60-68.
Fleurence RL. Cost-effectiveness of fracture prevention treatments in the elderly. *Int J Technol Assess Health Care*. 2004;20(2):184-191.

> Cost-effectiveness studies in which the effectiveness estimate was based on the findings from an outdated Cochrane Revie. The estimate conflicted with the updated Cochrane Review and with the most recent AHRQ report. In the study by Church et al., the vitamin analysis was for residential populations only but the effectiveness estimate was derived from community-dwelling individuals.

Jagannath VA, Fedorowicz Z, Asokan GV, Robak EW, Whamond L. Vitamin D for the management of multiple sclerosis. *Cochrane Database Syst Rev*. 2010;(12):CD008422.

> A Cochrane Review that identified only 1 RCT. One earlier RCT was missed and 1 new RCT plus an additional trial report were published after the search time frame of this Cochrane Review. Individual trials were reviewed for the current evidence report.

Thomas GN, Scragg R, Jiang CQ, et al. Hyperglycaemia and vitamin D: a systematic overview. *Curr Diabetes Rev*. 2012;8(1):18-31.

> A systematic review of vitamin D supplementation in patients with abnormal blood glucose that did not describe a systematic literature search, did not assess study quality, did not conduct any meta-analyses, and did not identify any eligible RCTs that were not included in the two selected systematic reviews. NOTE: This study was excluded from evidence considered for Key Questions #2b and #4b, but was referenced in the evidence described for Key Question #1.

Willis MS. The health economics of calcium and vitamin D3 for the prevention of osteoporotic hip fractures in Sweden. *Int J Technol Assess Health Care*. 2002;18(4):791-807.

> A cost-effectiveness study that used an effectiveness estimate based on a single study conducted among nursing home residents, while incidence rates were taken from a general community population.