



Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)

Executive Summary

Background

In 2009, the Tufts Evidence-based Practice Center (EPC) conducted a systematic review of the scientific literature on vitamin D and calcium intakes as related to status indicators and health outcomes. The purpose of this report was to guide the nutrition recommendations of the Institute of Medicine (IOM) Dietary Reference Intakes (DRIs).

In September 2007, the IOM held a conference to examine the lessons learned from developing DRIs, and future challenges and best practices for developing DRIs. The conference concluded that systematic reviews would enhance the transparency and rigor of DRI committee deliberations. With this framework in mind, the Agency for Healthcare Research and Quality (AHRQ) EPC program invited the Tufts EPC to perform the systematic review of vitamin D and calcium.

In May and September 2007, two conferences were held on the effect of vitamin D on health. Subsequently, a working group of scientists from the United States and Canadian Governments convened to determine whether enough new research had been published since the 1997 vitamin D DRI to justify an update. Upon reviewing the conference proceedings and results from a recent systematic review, the group concluded that sufficient new data beyond bone health had been published.

Areas of possible relevance included new data on bone health for several of the life stage groups, reports on potential adverse effects, dose-response relations between intakes and circulating 25-hydroxyvitamin D (25(OH)D)

Evidence-based Practice Program

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

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concentrations and between 25(OH)D concentrations, and several health outcomes. **Throughout the remainder of this summary and in the report, new text is presented in boldface type.**

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decisionmaking for vitamin D in primary care, which will include information from this updated systematic review on vitamin D and health outcomes, the ODS and AHRQ requested an update to the 2009 systematic review that will incorporate the findings of studies on vitamin D and vitamin D administered in conjunction with calcium that have been conducted since the release of the 2009 review. This updated report assesses all outcomes assessed in the original 2009 report (for vitamin D and vitamin D plus calcium) with the exception of outcomes pertaining to body weight and composition and postnatal growth. This updated report also describes the assay methodologies used in trials included in the original review as well as any newly included studies that report on the effect of vitamin D supplementation on serum 25(OH)D concentrations, to permit a comparison of dose-response outcomes by assay method. The text of the original 2009 report has been preserved essentially in its entirety: Text and tables that report outcomes of calcium supplementation only have been omitted. Here and in the remainder of the report, updated methods, study details, and findings are presented in boldface type. The protocol for the updated report was posted on the AHRQ Web site for public comment, which can be found at <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529>.

This update was requested by the sponsor in anticipation of a conference focused on the evaluation of evidence related to vitamin D and health outcomes, but the update can also be helpful to other stakeholders. The sponsor's interest was to determine whether the inclusion of newer relevant data that became available during the period following the close of the 2009 review would alter or continue to support the conclusions of the 2009 report. The sponsor's interest did not include the topic area of calcium alone or of growth and body weight as they relate to vitamin D, so for reasons of cost these components of the original report were not included in this review.

The **original** report included a systematic review of health outcomes relating to vitamin D and calcium intakes, both alone and in combination; **the current report updates that systematic review for outcomes relating to intakes of vitamin D alone or in combination with calcium.**

The executive summary provides a high-level overview of the findings of the systematic review; **the summary of studies included in the current report is in boldface type.** Recommendations and potential revisions of nutrient reference values (i.e., the new DRIs) based on this review are the responsibility of the IOM committee and are beyond the scope of this report.

Methods

This systematic review—**both the original and the update**—answers key scientific questions on how dietary vitamin D and calcium intakes affect health outcomes. Federal sponsors defined the Key Questions, and a technical expert panel was assembled to refine the questions and establish inclusion and exclusion criteria for the studies to be reviewed. In answering the questions, we followed the general methodologies described in AHRQ's "Methods Guide for Comparative Effectiveness Reviews." The **original** report was provided to an IOM committee charged with updating vitamin D and calcium DRIs. **The current report will be made available to NIH/ODS, which are the sponsors of this update. Neither this report nor the original makes clinical or policy recommendations.**

The population of interest is the "general population" of otherwise healthy people to whom DRI recommendations are applicable. The Key Questions addressed in **the original report** and this **updated** report are as follows:

Key Question 1. What is the effect of vitamin D, calcium (**excluded from current/updated report**), or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, body weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification (**the current report excludes the outcomes of postnatal growth and weight outcomes**)?

Key Question 2. What is the effect of vitamin D, calcium (**excluded from current report**), or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density?

Key Question 3. What is the association between serum 25(OH)D concentrations or calcium balance (**excluded from current report**) and clinical outcomes?

Key Question 4. What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations?

Key Question 5. What is the association between serum 25(OH)D concentrations and surrogate or intermediate outcomes?

The **original report** performed electronic searches of the medical literature (1969–April 2009) to identify publications addressing the aforementioned questions. We set specific eligibility criteria. We reviewed primary studies and existing systematic reviews. When a qualifying systematic review was available, we generally relied on the systematic review, and updated it by reviewing studies published after its completion. **The search strategy of peer-reviewed literature for the updated report duplicated that used in the original 2009 report to the extent possible, excluding the searches specific to calcium only and those for the outcomes of growth and weight. Searches for the current report covered the time period from January 2008 to April 2013.**

We rated the primary studies using a three-grade system (A, B, or C), evaluating each type of study design (i.e., randomized controlled trial or RCT, cohort, and nested case-control). Grade A studies have the least bias, and their results are considered valid within the limits of interpretation for that study design. Grade B studies are susceptible to some bias, but the amount is not sufficient to invalidate the results. Grade C studies have significant bias that may invalidate the results.

Results

The original report screened for eligibility a total of 18,479 citations that were identified through our searches, perusal of reference lists, and suggestions from experts. Of 652 publications that were reviewed in full text, 165 primary study articles and 11 systematic reviews were included in the systematic review. Their results are summarized in this report.

For the current report, we screened for eligibility a total of 6,165 citations identified through electronic searches, reference mining, and handsearches for articles suggested by experts. Of 1,107 publications reviewed in full text, 154 new articles (reporting on 156 studies) and two existing systematic reviews were included in this systematic review. The results are summarized in this report in boldface type. Table A summarizes the numbers of studies included for each outcome for both the original and the current report, stratified by study design, as well as the conclusions.

Vitamin D

Vitamin D and Growth

For the current report, we identified five new RCTs (reported in four articles) and two new observational studies that evaluated intake of or exposure to vitamin D, respectively, on birth weight and/or length. In the current report, five RCTs (reported in four articles) reported on the effect of vitamin D supplementation during pregnancy on birth weight and/or length. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400 international units (IU) vitamin D per day at 16 weeks gestation or earlier into three groups, who were given an additional 0, 1,600, or 3,600 IU vitamin D per day through the remainder of gestation; the study found no difference in birth weight among interventional arms (rated A).¹ The second study, a pseudo-RCT conducted in India, divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D and the other received two doses of 3,000 micrograms vitamin D (a group of untreated women who were 24 weeks pregnant or more served as the controls); both of the treated groups gave birth to infants who were significantly heavier than the usual care group ($p=0.003$) (rated C). The third RCT, the AViDD study conducted in Bangladesh, randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000 IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes (rated A). For the fourth and fifth studies, data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D₃ Supplementation studies—in which pregnant women were randomized to receive 0, 2,000, or 4,000 IU vitamin D per day in addition to their prenatal vitamins—were analyzed in combination: No differences were observed in birth weight among the groups (rated B). Of the two observational cohort studies, one observed a significant association of second trimester maternal vitamin D concentrations (rated B) and one found no association (rated A).

As reviewed in the original report, six RCTs, one nonrandomized comparative intervention study, and two observational studies evaluated intake of vitamin D or serum 25(OH)D concentrations and growth parameters in infants and children. The studies had diverse populations and methodological approaches. One RCT and one observational study were rated B; seven studies were

rated C. Most studies found no significant associations between either maternal or offspring vitamin D intake and offspring's weight or height, but two C-rated intervention studies from the same center in India found a significant effect of total maternal vitamin D intake of 1.2 million IU and increased infant birth weights.

Vitamin D and Cardiovascular Events

One good-quality existing systematic review of prospective studies identified for the current report found a significant association between low serum 25(OH)D concentrations and a number of clinical cardiovascular outcomes, including total cardiovascular disease, coronary heart disease, cardiovascular disease mortality, and stroke. No RCTs were identified for the current report that evaluated the effects of vitamin D on clinical cardiovascular disease outcomes. New observational studies identified for the current report (7 for total cardiovascular events, 17 for cardiovascular death, 2 for ischemic heart disease, 6 for myocardial infarction, 8 for stroke, and 3 for fatal stroke) found mixed associations between 25(OH)D and all of these outcomes.

As reviewed in the original report, one B-rated RCT and four cohort studies (two rated A, two C) have analyzed the association between serum 25(OH)D concentrations and risk of cardiovascular events. The RCT, which compared vitamin D₃ (100,000 IU every 4 months) or placebo for 5 years in elderly people, found no significant difference in event rates for various cardiovascular outcomes, including total events and cardiovascular deaths. In two of the cohort studies, significant associations were found between progressively lower 25(OH)D concentration—analyzed at upper thresholds of 37.5 and 75 nmol/L—and progressively increased risk of any cardiovascular event. The other two cohort studies found no significant associations between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke.

Vitamin D and Body Weight

The current report did not assess the association between vitamin D and body weight. For the original report, no studies evaluated serum 25(OH)D concentrations and risk of obesity or overweight. We evaluated only RCTs for changes in body weight. Three RCTs (one rated B, two rated C) compared a range of dosages (300 IU/d to 120,000 IU every 2 weeks) to placebo. Vitamin D supplementation had no significant effect on weight.

Vitamin D and Cancer

Cancer From All Causes

No new RCTs were identified for the current report that addressed the effect of vitamin D or vitamin D combined with calcium on the risk for total cancer or cancer mortality. Two new cohort studies found no association between total (all-cause) cancer incidence and serum 25(OH)D concentrations (rated A and B). Ten new cohort studies and one new nested case-control study addressed the association of serum 25(OH)D concentrations and cancer mortality. Five of the cohort studies (one rated A, four rated B) observed no association of serum 25(OH)D concentration with total cancer mortality. Three cohort studies and the nested case-control study observed a trend toward increased risk with decreased serum 25(OH)D (all rated B). One analysis using updated Third National Health and Nutrition Examination Survey (NHANES III) data (rated B) observed a trend toward increasing risk for death with increasing serum 25(OH)D among men at higher latitudes whose blood was drawn in summer but the reverse in women. One cohort study observed a U-shaped association of increasing mortality with both low and high serum 25(OH)D.

The original report identified two B-rated RCTs and an analysis of the NHANES database (two publications, rated B and C). Both RCTs were conducted in older adults (postmenopausal women in one and people >70 years in the other). They found no significant effects for vitamin D supplementation (approximately 1,500 IUs per day or 100,000 IU every 4 months). Analyses of NHANES III showed no significant association between baseline serum 25(OH)D concentrations and total cancer mortality.

Prostate Cancer

In the current report, four new nested case-control studies (two rated A, two rated B) and one new prospective cohort study (rated B) found no association between baseline serum 25(OH)D concentrations and risk for prostate cancer. Two new nested case-control studies (both rated B) observed a trend between higher serum vitamin D concentrations and increasing risk for prostate cancer. In one study this increase was seen only among men whose sera were sampled in summer or autumn; in the other study, this trend was observed only when participants were divided by quartiles of 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency (concentrations less than 50 nmol/L being considered

deficient, 50–75 nmol/L insufficient, and 75–125 nmol/L considered sufficient).

In the original report, 12 nested case-control studies (3 rated B, 9 C) evaluated the association of baseline serum 25(OH)D concentrations and prostate cancer risk. No eligible RCTs were identified. Eight of the nested case-control studies found no statistically significant dose-response relationship between serum 25(OH)D concentrations and the risk of prostate cancer. One C-rated study found a significant association between lower baseline serum 25(OH)D concentrations (<30 compared with >55 nmol/L) and higher risk of prostate cancer. Another C-rated study suggested the possibility of a U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer (i.e., lower and higher serum 25(OH)D concentrations were associated with an increased risk of prostate cancer compared with that of the in between reference level).

Colorectal Cancer

No new RCTs and cohort studies that addressed the effect of vitamin D on colorectal cancer mortality or incidence were identified for the current report. Three new nested case-control studies (two rated A, one rated B) found trends of increasing colorectal cancer incidence with decreasing 25(OH)D concentrations. One nested case-control study (rated B) found no association between colorectal cancer and 25(OH)D. Two of these nested case-control studies (both rated B) also examined colon and rectal cancer as separate outcomes. One study reported a significant negative trend between 25(OH)D and colon cancer risk and the other found a nonsignificant negative trend. For rectal cancer, the same two studies reported either a negative trend or a small but nonsignificant negative trend with 25(OH)D.

The original report identified one B-rated RCT, one B-rated cohort study, and seven nested case-control studies (five rated B, two C) that evaluated the association between vitamin D exposure and colorectal cancer. The RCT of elderly population reported no significant difference in colorectal cancer incidence or mortality with or without vitamin D₃ supplements over 5 years of followup. Most nested case-control studies found no significant associations between serum 25(OH)D concentrations and risk of colorectal cancer incidence or mortality. However, two of the three B-rated nested case-control studies in women found statistically significant trends between higher serum 25(OH)D concentrations and lower risk of colorectal cancer, but no individual quantile of serum 25(OH)

D concentration had a significantly increased risk of colorectal cancer (compared with the reference quantile). The B-rated cohort study of women also suggested an association between higher serum 25(OH)D concentrations (>50 nmol/L) and lower risk of colorectal cancer mortality. The studies of men or of both sexes, and of specific cancers, did not have consistent findings of associations.

Colorectal Polyps

No new studies were identified for the current report that assessed the association between colorectal polyps and serum concentrations of 25(OH)D.

For the original report, one B-rated nested case-control study in women found no significant association between serum 25(OH)D concentrations and risk of colorectal polyps. No RCTs evaluated this outcome.

Breast Cancer

Eight new observational studies that assessed the association between 25(OH)D and breast cancer were identified for the current report. Two cohort and four nested case-control studies found no association (three rated A, three rated B). Two nested case-control studies found increasing risk of breast cancer with decreasing 25(OH) concentrations (both rated B).

One new observational study that assessed the association between 25(OH)D and breast cancer-specific mortality was also identified. This cohort study found no association (rated B).

Two new studies, an RCT that examined the effect of vitamin D and calcium intake on breast density and a nested case-control study that assessed the association of serum 25(OH)D with breast density, were identified. The RCT found a decrease in percent mammographic density among women who had greater than or equal to 400 IU per day total vitamin D intake (rated A). The nested case-control found lower risk of increased mammographic density with 25(OH) concentrations above the first quartile (rated B).

In the original report, one cohort compared serum 25(OH)D concentrations and the risk of breast cancer mortality, and two nested case-control studies compared 25(OH)D concentrations and the incidence of breast cancer. All three studies were rated B. The NHANES III analysis reported a significant decrease in breast cancer mortality during 9 years of followup in those with baseline serum 25(OH)D concentration greater than 62 nmol/L. However, during 7 to 12 years of followup, the nested case-control studies found no significant relationship between serum

25(OH)D concentration and risk of breast cancer diagnosis in either premenopausal or postmenopausal women.

Pancreatic Cancer

For the current report, a new pooled nested case-control study within eight cohorts found an association between 25(OH)D concentration and pancreatic cancer (rated B). Individuals with 25(OH)D concentration greater than or equal to 100 nmol/L had greater risk of pancreatic cancer incidence compared with those with 25(OH)D less than 25 nmol/L.

For the original report, two A-rated nested case-control studies evaluated the association of serum 25(OH)D concentrations and pancreatic cancer. No relevant RCTs were identified. One study of male smokers found a statistically significant relationship between increasing serum 25(OH)D concentration (>65.5 vs. <32 nmol/L) and higher risk for pancreatic cancer, and the subanalysis of the second study found an increased risk of pancreatic cancer among study participants with higher 25(OH)D concentrations (>78.4 nmol/L) compared with lower (<49.3 nmol/L) concentrations only in those living in low residential ultraviolet B exposure areas.

Vitamin D and Immunologic Outcomes

The current report identified four new RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and nine cohort studies that assessed the association between serum 25(OH)D concentrations and risk for infectious illnesses. RCTs of infants and adults reported no significant effect of supplementation on the risk for upper respiratory infections (one rated A; three rated B). Three new prospective cohort studies observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory infections at 3 to 6 months of age, in New Zealand, China, and the Netherlands, respectively (all rated B). Two studies of school-age children observed inverse associations of serum 25(OH)D and risks for various infectious illnesses (both rated B). (“Inverse association” refers to an association between lower serum 25(OH)D concentrations and a higher risk for the outcome of interest; “association” or “positive association” refers to an association between higher serum 25(OH)D concentration and a higher risk for the outcome.) A study of healthy U.S. adults found an association between serum concentrations of 25(OH)D levels of 95 nmol/L or higher and reduced risk for acute respiratory viral infections (rated B). One study of adults observed an inverse association of serum 25(OH)D with risk for respiratory disease mortality, and another observed an inverse association with risk for pneumonia (both rated B).

The report identified one new RCT that found no effect of prenatal vitamin D supplementation on the risk for wheeze, atopy, and eczema (rated A). The report also identified five new prospective cohort/nested case-control studies that reported mixed associations of serum concentrations of 25(OH)D and risk for asthma, atopy, and/or eczema. An Australian study observed a significant association of cord blood 25(OH)D and risk for eczema but not allergies at 12 months of age. A prospective cohort study conducted in the United Kingdom found no association between maternal serum 25(OH)D at 34 weeks gestation and asthma, wheeze, and atopy in their children at 6 years of age. A prospective cohort study conducted in the Netherlands found that serum 25(OH)D concentrations at 4 years of age significantly predicted asthma and severe asthma at 8 years of age. Another United Kingdom longitudinal study found a small but statistically significant association of wheeze and antecubital dermatitis in 10-year old children with serum levels of 25(OH)D₂ but a negative association with 25(OH)D₃. Finally, the HUNT study, a large population health survey in Norway, found no association of vitamin D with asthma in women and only a weak association in men that disappeared when adjusted for confounders.

The current report identified one new RCT and four new prospective cohort studies on the risk for autoimmune disease. A substudy of the Women’s Health Initiative (WHI) calcium/vitamin D (CaD) trial found no effect of supplementation on women’s risk for rheumatoid arthritis (rated A). Two nested case-control studies and one cohort study assessed the association between maternal serum 25(OH)D concentrations or subsequent childhood or adult concentrations with risk for type 1 diabetes mellitus and reported mixed findings (one each rated A, B, and C). One study assessed the effects of maternal serum 25(OH)D concentrations on the risk for multiple sclerosis (MS) in the offspring and also assessed the effect of serum 25(OH)D concentrations across the adult population on the risk for subsequent MS and found mixed effects (rated B).

For the original report, two C-rated cohort studies, but no RCTs, evaluated immunologic outcomes. NHANES III found no significant association between serum 25(OH)D concentrations and infectious disease mortality. Another cohort study suggested a possible relationship between higher maternal 25(OH)D concentration (>50 nmol/L) and increased risk of eczema in their children, but the analysis did not control for important confounders, and the 25(OH)D concentrations in the children were not measured.

Vitamin D and Pregnancy-Related Outcomes

Preeclampsia

For the current report, we identified one article that reported on two combined RCTs assessing the effect of supplemental vitamin D on the risk for preeclampsia: Supplementation with 4,000 IU per day decreased the risk for preeclampsia. We also identified five new nested case-control studies and two prospective cohort studies (all rated B), of which three of the nested case-control studies and the two prospective case-control studies observed an association between 25(OH)D concentrations less than 50 nmol/L and preeclampsia or severe preeclampsia. The other two nested case-control studies (the Canadian EMMA study and a U.S. study) observed no association between low first trimester maternal 25(OH)D levels and severe preeclampsia.

In the original report, one B-rated nested case-cohort study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia.

Other Outcomes

In the current report, we identified two new cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one new nested case-control study and one prospective cohort study that assessed the association with preterm birth. One of the two cohort studies found an increase in the incidence of SGA at the lowest concentration range of maternal serum 25(OH)D compared with higher serum vitamin D concentrations for both white and black mothers (study rated B). The other cohort study, which assessed 412 mother-infant pairs, found a U-shaped association between serum 25(OH)D and incidence of SGA among white mothers. The lowest risk was observed from 60 to 80 nmol/L; compared with serum 25(OH)D 37.5–75 nmol/L, SGA odds ratios (95% CI) for levels, 37.5 and 0.75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8); this association was not seen among black mothers (study rated A).

The nested case-control study that assessed the association with preterm birth found no significant association (rated B), whereas the prospective cohort study did observe an association between lower prenatal serum 25(OH)D concentrations and the risk for preterm birth among women carrying twins (rated A).

We found no new studies for the current report on the relationship of maternal serum 25(OH)D and pregnancy hypertension.

The original report did not identify any eligible studies on the relationship of vitamin D and maternal hypertension, preterm birth, or small infant for gestational age.

Vitamin D and Bone Health

The results reported in this section are based on the Ottawa EPC Evidence Report “Effectiveness and safety of vitamin D in relation to bone health” and on our updated literature review of studies published after its completion.

Rickets

No new studies assessing the association between vitamin D supplementation and the risk for rickets met the inclusion criteria for the current report.

The original report cited the Ottawa EPC report for these outcomes. The Ottawa EPC report concluded that there is “fair” evidence, regardless of the type of assay, for an association between low serum 25(OH)D concentrations and confirmed rickets. According to the report, there is inconsistent evidence regarding the threshold concentration of serum 25(OH)D, above which rickets does not occur.

Our updated search did not identify new studies examining the association between vitamin D and rickets.

Fractures, Falls, or Performance Measures of Strength

The current report did not identify any new RCTs that assessed the effect of interventions of vitamin D alone on fracture risk. We identified two new RCTs that examined the effect of supplementation with vitamin D on the risk for falls, two new RCTs on muscle strength, and six new observational studies that assessed the association between serum 25(OH)D and fracture risk; results were inconsistent among them.

Two RCTs were identified for the current report that examined the effects of vitamin D supplementation on the risk for falls among older adults (both rated A). One trial found a small effect, and one found reductions only in particular groups of fallers.

Two RCTs were identified for the current report that examined the effects of 1 year of vitamin D supplementation on muscle strength (both rated A). One RCT showed positive effects among older adults, and one study showed effects only among the participants with lower serum 25(OH) D concentrations at baseline.

Four prospective cohort studies assessed the association between serum 25(OH)D concentrations and muscle strength, and one prospective cohort study assessed the association between serum 2(OH)D and falls. Three of the four prospective cohort studies reported associations between lower serum 25(OH)D and decreased or decreasing muscle strength and performance (one rated A, one rated B, one rated C); a fourth cohort study saw no association with faster rate of decline in muscle function (rated B). An association was seen between lower 25(OH)D concentrations and increased risk for falls over a year (study rated B).

We identified eight prospective cohort and nested case-control studies that assessed the association between 25(OH)D status and fracture risk. Three studies that assessed risk for hip fracture at 6 to 11 years followup (one rated A and two rated B) had mixed results.

Two large-scale studies with B ratings, one among older men and one among older adults of both sexes, found no association of serum 25(OH)D concentration and risk for nonvertebral fracture. Followups to two other large-scale studies, both with A ratings, reported serum 25(OH)D to be a significant predictor of hip fracture and other major osteoporotic fractures in older adults.

Two studies that assessed total fragility fracture (one rated A and one rated B), both in postmenopausal women, also reported inconsistent results.

As described in the original report, the Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures of strength among postmenopausal women or elderly men are inconsistent.

Findings from three additional C-rated RCTs reported no significant effects of vitamin D supplementation (dosage range 400–822 IU/d) in reducing the risk of total fractures or falls in adults older than 70 years.

Bone Mineral Density or Bone Mineral Content

To assess the effect of vitamin D on bone mineral content or density, we included only RCTs. Eight new RCTs identified for the current report assessed the effects of supplemental vitamin D alone on bone mineral content (BMC) or density (BMD). One of the eight, a study in infants (rated A), showed a trend toward increasing BMC. A second study, in postmenopausal women, found that 1,000 IU vitamin D per day reduced loss of BMD at the hip compared with no or 400 IU per day supplementation, but no effect was seen on spinal BMD (study rated A). Six RCTs, two in teen girls and the remaining four in adults of both sexes

(one rated A, four rated B, and one rated C) showed no effect of vitamin D supplementation for as much as 2 years on BMD.

As described in the original report, the Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents (6 months through 18 years old). In addition, there was “fair” evidence among observational studies of postmenopausal women and elderly men to support an association between higher serum 25(OH)D and higher BMD or increases in BMD at the femoral neck. However, there was discordance between the results from RCTs and the majority of observational studies.

For this outcome, we included only RCTs for our update literature review. Consistent with the findings of RCTs in the Ottawa EPC report, the three additional RCTs (one rated A, one B, one C) showed no significant effects of vitamin D supplementation on BMC in children or BMD in adults.

Vitamin D and All-Cause Mortality

No new RCTs were identified for the current report that assessed the effect of vitamin D supplementation on risk for all-cause mortality. The current report identified 25 new articles that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, 7 found no association (1 rated A, 6 rated B), 16 found an association of lower serum 25(OH)D concentrations with increased risk for mortality (6 rated A, 9 rated B: 1 article reported on 2 studies), and 2 reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk (rated A and B).

The assessment of the literature on vitamin D and all-cause mortality in the original report was based on a reanalysis of an existing systematic review and metaanalysis of RCTs on vitamin D supplementation for mortality. One additional C-rated RCT was identified. Four additional cohort studies (one rated B, three C) on the association of vitamin D and all-cause mortality also qualified. Four RCTs (N=13,899) were included in the reanalysis of the systematic review. In each study, mean age was older than 70 years and dosages ranged between 400 to 880 IU per day. Vitamin D supplementation had no significant effect on all-cause mortality (summary relative risk [RR]=0.97, 95% CI 0.92, 1.02; random effects model). There is little evidence for between-study heterogeneity in these analyses. Three of the cohort studies found no significant association between 25(OH)D concentrations

and all-cause mortality, but one found a significant trend for lower odds of death with increasing 25(OH)D concentrations, greater than 23 nmol/L in men and greater than 19 nmol/L in women.

Vitamin D and Hypertension and Blood Pressure

Hypertension

For the current report we identified no new RCTs that addressed the relationship of serum 25(OH)D concentrations or supplementation with hypertension. A large prospective cohort study identified for the current report that evaluated the association between serum 25(OH)D concentration and the risk for hypertension using the Intermountain database found a highly significant association of very low and low baseline serum 25(OH)D concentrations and the prevalence of hypertension at an average of 1.3 years followup (rated C). The Intermountain data were analyzed with 25(OH)D cutoff points of 37.5 and 75 nmol/L. Significant associations were identified for those with serum concentrations below 75 nmol/L. An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians' Health Study (men of average age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile (rated A).

The original report identified no relevant RCTs. In a B-rated combined analysis of the Health Professionals Followup Study and the Nurses' Health Study, significantly higher incidence of hypertension at 4 years was found in men and women (mostly within the 51 to 70 year old life stage) with serum 25(OH)D concentrations less than 37.5 nmol/L, compared with those with higher 25(OH)D concentrations. At 8 years, a similar significant association was found for men but not for women.

Blood Pressure

The current study identified 10 new RCTs that assessed the effects of 1 or more dosage levels of vitamin D compared with placebo on blood pressure in adults. Dosages ranged from 125 IU to 5700 IU per day. Followup ranged from 3 months to 1 year. Participants included postmenopausal women; middle-aged U.S. blacks (rated A); overweight young Chinese and Dutch adults; healthy South Asian women residing in the United Kingdom; and healthy young women

from Spain. Of the 10 RCTs, no effect of vitamin D supplementation was observed in 7 (5 rated A and 2 rated B); vitamin D significantly decreased systolic blood pressure in 2 studies (both systolic and diastolic in one of the studies) (rated B); and in the final study, systolic blood pressure actually increased slightly in the supplemented group (rated C).

The original report evaluated only RCTs for changes in blood pressure. Three RCTs of vitamin D versus placebo (one rated A, two B) evaluated blood pressure outcomes. The trials used a range of vitamin D dosages (800 IU/d to 120,000 IU every 2 weeks), with or without supplemental calcium in both groups. All trials reported no significant effect on diastolic blood pressure, but the effect upon systolic blood pressure was inconsistent. The three trials found either a net reduction, no change, or a net increase in systolic blood pressure with vitamin D supplementation after 5–8 weeks.

Combined Vitamin D and Calcium

Combined Vitamin D and Calcium and Growth

The current report did not consider growth as an outcome, except for prenatal growth. No new studies were identified. In the original report, one C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth.

Combined Vitamin D and Calcium and Cardiovascular Events

For the original study, a variety of cardiovascular events after 7 years were evaluated in the WHI trial of combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) (CaD) versus placebo in postmenopausal women. This study was rated B. No significant effect was found with combined vitamin D and calcium supplementation on any cardiovascular outcome. However, borderline nonsignificant associations were found for three outcomes, suggesting increased risk with supplementation for a composite cardiac outcome, invasive cardiac interventions, and transient ischemic attacks. No significant associations were found for a composite cardiac outcome, coronary heart disease death, myocardial infarction, hospitalization for heart failure, angina, stroke or transient ischemic attack, and stroke alone.

The current report identified only one new study that assessed the effects of vitamin D and calcium supplements combined on cardiovascular events: A post hoc analysis of the WHI CaD trial that stratified participants on the basis of personal supplement use before and during the trial found no impact of the study supplements alone (either positive or negative) on risk for cardiovascular events (rated A).

Combined Vitamin D and Calcium and Body Weight

This outcome was not investigated for the current report. For the original report, no studies evaluated the risk of obesity or overweight. Only RCTs were evaluated for changes in body weight. Two RCTs (rated B and C) were identified that evaluated the effects of combined vitamin D and calcium supplementation on body weight in the setting of either an energy neutral diet or an energy restricted diet. Both used vitamin D 400 IU per day and calcium carbonate (1,000 mg/d or 1,200 mg/d) and were restricted to women. The B-rated WHI trial, after 7 years, found a highly significant ($P=0.001$), but clinically questionable net difference of 0.13 kg between the supplemented and placebo groups. In a small C-rated trial, after 15 weeks, those overweight women on supplement lost 4 kg and those on placebo lost 3 kg. This difference was not statistically significant.

Combined Vitamin D and Calcium and Cancer

Total Cancer

No new studies were identified for the current report on the association of combined vitamin D and calcium intake with any cancer outcomes. However, as described below, data from the WHI calcium and vitamin D (CaD) trial were reanalyzed.

Two RCTs (rated B and C) **identified for the original report** reported effects of combined vitamin D and calcium supplementation on the risk of total cancer. The RCTs reported inconsistent results. The B-rated WHI trial (vitamin D 400 IU/d and calcium 1,000 mg/d) showed no effects while the B-rated trial (vitamin D 1,000 IU/d and calcium 1,400–1,500 mg/d) reported a significant reduction of total cancer risk. However, baseline serum 25(OH)D concentrations were substantially different between these two trials (42 nmol/L [WHI] versus 72 nmol/L).

Colorectal Cancer

Only the B-rated WHI trial **identified for the original report** evaluated colorectal cancer. It reported no significant reduction in colorectal cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1,000 mg/d) compared with placebo. **A post hoc**

analysis of the WHI CaD trial identified for the current report that stratified participants by baseline use of personal vitamin D and calcium supplements found no difference in risk for colorectal cancer by previous or additional supplement use.

Colorectal Polyps

The B-rated WHI trial **identified for the original report** was the only trial of combined vitamin D₃ and calcium supplements to evaluate colorectal polyps. It found no significant effect of supplementation on colorectal polyp incidence. A B-rated subgroup analysis of a secondary prevention trial of adenomatous adenoma reported that people taking calcium supplements (1200 mg/d) who had higher baseline serum 25(OH)D concentrations (>72.6 nmol/L) had significantly lower risk of relapse compared with placebo. In contrast, among people with lower baseline serum 25(OH)D concentrations, there was no significant difference in relapse rates between those taking calcium supplements or placebo ($P=0.01$ for interaction between calcium supplementation and 25(OH)D concentration).

Breast Cancer

Only the B-rated WHI trial evaluated breast cancer. It reported no significant reduction in breast cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) compared with placebo. **A post hoc analysis of the WHI CaD trial identified for the current report that stratified participants by baseline use of personal vitamin D and calcium supplements found a trend toward a reduction in risk for breast cancer among women in the intervention group who had not been using personal supplements at baseline.**

Combined Vitamin D and Calcium and Preeclampsia, Hypertension in Pregnancy, and Preterm Birth or Small Infant for Gestational Age

Preeclampsia

No new studies were identified for the current report that assessed this outcome. In the original report, one C-rated RCT found no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) supplementation on prevention of preeclampsia.

Other Outcomes

No studies evaluated the relationship of vitamin D with or without calcium and pregnancy-related high blood pressure, preterm birth, or small infant for gestational age.

Combined Vitamin D and Calcium and Bone Health

The results reported in this section are based on the Ottawa EPC Evidence Report “Effectiveness And Safety of Vitamin D in Relation to Bone Health” and on our updated literature review of studies published after its completion.

Rickets, Fractures, Falls, or Performance Measures

For the current report, we identified no new studies on the effect of vitamin D and calcium supplementation on rickets that met the inclusion criteria.

The current report identified one new RCT and one reanalysis of the WHI CaD trial that examined the effect of an intervention with vitamin D and calcium on osteoporotic fracture risk among postmenopausal women. The reanalysis of data from the WHI CaD trial compared the effects of the intervention between women who had been using personal vitamin D and/or calcium supplements at baseline. The primary outcome was risk for hip fracture at 5 or more years and secondary outcomes included other fractures. The reanalysis found that among women who were not taking calcium or vitamin D supplements at baseline, the risk for hip fracture was significantly decreased (no effect was seen among women who had been taking supplements); it found no effect of the intervention on overall fracture risk in women who had been taking supplements or in those who had not (rated A).² The second RCT, the OSTPRE study, found no effect of 3 years’ supplementation with calcium and vitamin D on risk for total, nonvertebral, distal forearm, upper extremity, or lower extremity fragility fractures among 3,195 postmenopausal women age 65 to 71 years (rated A).

One RCT on middle-age and older Australian men (age 50 to 79) tested the effect of an 18-month intervention of daily vitamin D (800 IU) and calcium (1,000 mg) on measures of muscle function (rated A). No effect was seen on any measure of muscle function, including step test, gait speed, or sway.

We identified one new RCT that assessed effects of supplementation on risk for falling: This study found no effect of the intervention (study rated C).

As described in the original report, the Ottawa EPC report concluded that supplementation with vitamin D (most studies used D₃) plus calcium is effective in reducing fractures in institutionalized populations, but evidence that supplemental vitamin D reduces falls in postmenopausal women and older men is inconsistent.

One study published after the Ottawa EPC report analyzed the performance measure outcomes in a small sample of postmenopausal women from the WHI trial. After 5 years, the study found generally no differences in performance measures between the groups taking vitamin D (400 IU/d) plus calcium (1,000 mg/d) supplementation or placebo. One RCT of premenopausal women (aged 17–35 years) found that vitamin D (800 IU/d) in combination with calcium (2,000 mg/d) supplementation reduced the risk of stress fracture from military training compared with placebo.

Bone Mineral Density or Bone Mineral Content

Of the seven new RCTs identified for this report on the effect of vitamin D and calcium supplementation on bone density or content, two studies were in girls (rated B) or young women (rated A): Both showed positive effects on BMC and BMD, respectively. Four of the RCTs enrolled postmenopausal women (one rated A, two rated B, and one rated C): All showed some positive effects, but the effects differed across the studies in the areas that were positively affected. One intervention that enrolled men showed no effects (rated A). Followup times ranged from 1 to 6 years. Vitamin D supplementation ranged from 200 to 800 IU per day, with calcium ranging from 600 to 1200 mg per day.

As described in the original report, the Ottawa EPC report concluded that overall, there is good evidence that combined vitamin D₃ and calcium supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip. In RCTs among (predominantly) postmenopausal women, vitamin D₃ (<800 IU/d) plus calcium (500 mg/d) supplementation resulted in small increases in BMD of the spine, the total body, femoral neck and total hip.

For this outcome, only RCTs were included for the update literature review. Three new RCTs (two rated B, one C) were identified that evaluated BMD outcomes. Two of the trials showed significant improvement in BMD in postmenopausal women receiving vitamin D₂ (300 IU/d) or D₃ (1,200 IU/d) plus calcium (1,200 mg/d) compared with placebo.

One C-rated RCT evaluated BMC outcomes in healthy girls (aged 10–12 years). Compared with placebo, there was no significant effect of supplementation with vitamin D₃ (200 IU/d) plus calcium (1,000 mg/d) on BMC changes.

Combined Vitamin D and Calcium and All-Cause Mortality

No new studies were identified for the current report that addressed this question. For the original report, an existing systematic review and metaanalysis of 18 RCTs on vitamin D supplementation for mortality was reanalyzed. No additional RCTs were identified. Eleven RCTs (N=44,688) of combined vitamin D (300–800 IU/d) and calcium (500–1,200 mg/d) supplementation met inclusion criteria for our reanalysis. The metaanalysis found no significant relationship between combined supplementation of vitamin D and calcium and all-cause mortality (RR=0.93, 95% CI 0.86, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses. Among eight RCTs (N=44,281) in postmenopausal women, there was no significant effect of supplementation on all-cause mortality.

Combined Vitamin D and Calcium and Hypertension and Blood Pressure

No new studies were identified for the current report that addressed this question. For the original report, only the B-rated WHI trial evaluated the risk of developing hypertension. Among the subset of women without hypertension at baseline, at 7 years the trial found the combined supplementation had no effect on incident hypertension. Only RCTs were evaluated for changes in blood pressure. Two trials (one rated B, one C) tested combined vitamin D (400 IU/d) and calcium (1,000 or 1,200 mg/d) and blood pressure. Both found no significant effect of supplementation on blood pressure after 15 weeks or 6.1 years.

How Does Dietary Intake of Vitamin D From Fortified Foods and Vitamin D Supplementation Affect Serum 25(OH)D Concentrations (Arrow 4)?

The results reported in this section are based on the Ottawa EPC Evidence Report “Effectiveness and safety of vitamin D in relation to bone health,” on our updated literature review of studies published after its completion, **on new studies identified for the current report, and on a high-quality systematic review published since the original report.**

The current report identified 1 new existing systematic review published since the original report that addressed the question as well as 18 new RCTs that met the inclusion criteria (2 that used fortified foods and the remainder that used supplements). The systematic review, based on 76 RCTs, reported widely varying

increases in serum concentrations of 25(OH) for similar doses of vitamin D, with a general increase in serum concentration with supplement administration. Of the RCTs identified for the current report that met the criteria for inclusion in an assessment of dose response, all reported increases in serum 25(OH)D with supplementation; however, the findings varied by age group and health status of participants, baseline serum 25(OH)D concentration, dose, duration, and assay used to assess serum 25(OH)D. Only one study used the National Institute of Standards and Technology vitamin D as a reference standard, and six reported participating in the Vitamin D External Quality Assessment Scheme. Of 54 RCTs included in the original and the current report, only 4 reported the year the assays were conducted.

As described in the original report, the Ottawa EPC report concluded that there is “good” evidence that dietary intake of vitamin D increases serum 25(OH)D concentrations among adults. Our updated search did not identify new RCTs on dietary intakes of vitamin D from fortified foods.

We graphically evaluated the net changes in serum 25(OH)D concentration against the doses of vitamin D supplementation using data from 26 RCTs with 28 comparisons in adults. Only RCTs of daily vitamin D₃ supplementation (doses ranged from 200 to 5000 IU/d) alone or in combination with calcium supplementation (doses ranged from 500 to 1550 mg/d) that provided sufficient data for the calculations were included. The relationship between increasing doses of vitamin D₃ with increasing net change in 25(OH)D concentration was evident in both adults and children. It was also apparent that the dose-response relationships differ depending on study participants’ serum 25(OH)D concentrations (≤ 40 vs. >40 nmol/L) at baseline, and depending on duration of supplementation (≤ 3 vs. >3 months).

Stratification of Key Outcomes by Vitamin D Assay Method

In addition to plotting the data for Vitamin D dose-response by the method used to assay serum 25(OH)D (Figure 15), for all outcomes reported in three or more RCTs or seven or more observational studies, we stratified the studies according to the assay method used to assess serum 25(OH)D concentrations (radioimmunoassay, radioreceptor/ligand assay, enzyme-linked immunoadsorption assay, chemiluminescence assay, and HPLC-tandem^a

^aHPLC is high pressure liquid chromatography

mass spectrometry). These stratified tables appear in Appendix H of the full report.

Outcomes for Tolerable Upper Intake Levels

We included only clinical outcomes of tolerable upper intake levels, such as all-cause mortality, cancer (incidence and mortality), soft tissue calcification, renal outcomes, and adverse events reported in RCTs. Results of all-cause mortality and cancer have been described in previous sections.

Renal Outcomes

As described in the original report, the WHI trial (vitamin D₃ 400 IU in combination with 1,000 mg calcium carbonate vs. placebo) found an increase in the risk of renal stones. No other study was identified that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

For the current report, two new studies assessed the occurrence of nephrolithiasis among participants in RCTs that administered approximately 1,100 and 2,000 IU per day supplemental vitamin D without calcium. No incidents of nephrolithiasis were reported in either study.

Adverse Events Reported in RCTs

The **original report noted that** reporting of adverse events in RCTs was generally inadequate, and most trials were not adequately powered to detect adverse events. Among the 63 RCTs included in the original report, 47 did not report information on adverse events.

Among 18 new RCTs included in the current study, most did not include any information on adverse events. One study, which administered 2000 or 4000 IU per day to women during the third trimester of pregnancy reported no adverse events. Three studies reported on only one specific outcome, hypercalcemia/serum calcium, or reported on this outcome and stated that no other adverse events were reported. Supplementation ranged from 400 to 5000 IU per day in these studies; only 1 case of hypercalcemia was reported across all 4 of the studies, in a trial that administered 1000 IU per day plus 1000 mg calcium. Five other studies that assessed hypercalcemia also reported no cases.

Five new studies reported on gastrointestinal symptoms, of which only one included supplemental calcium. Two new studies reported on serious adverse events, including one death, cancer diagnoses, and acute surgeries, which were more prevalent in the placebo

group and thus could not have been related to the use of vitamin D.

In the original report, 5 RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods. Eleven RCTs reported at least one adverse event. Excessive gas, bloating, and gastrointestinal discomforts were reported to be associated with calcium supplementation (doses ranged from 600 to 1000 mg/d). Other RCTs of vitamin D (doses ranged from 400 to 5,714 IU/d vitamin D₃ or ranged from 5000 to 10,000 IU/d vitamin D₂) and/or calcium supplementations (doses ranged from 200 to 1,500 mg/d) reported few cases of gastrointestinal disruption (such as constipation, diarrhea, or upset stomach), musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi. However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study.

Summation

The **original** systematic review identified 165 primary study articles and 11 systematic reviews (which incorporated over 200 additional primary articles) that met the eligibility criteria established by the Technical Expert Panel. **The current study identified 154 new articles (reporting 156 studies) and two systematic reviews that met the eligibility criteria.** Despite the relatively large number of studies included, with the following few exceptions, it is difficult to make any substantive statements on the basis of the available evidence concerning the association of either serum 25(OH) D concentration, vitamin D supplementation, calcium intake, or the combination of both nutrients, with the various health outcomes because most of the findings were inconsistent.

In general, **the original report found that** among RCTs of hypertensive adults, calcium supplementation (400–2,000 mg/d) lowered systolic, but not diastolic, blood pressure by a small but statistically significant amount (2–4 mm Hg). **The current report did not address calcium supplementation alone.**

For **adult** body weight, despite a wide range of calcium intakes (from supplements or from dairy and nondairy sources) across the calcium trials, the RCTs **identified for the original report** were fairly consistent in finding no significant effect of increased calcium intake on body weight. **The current report addressed body weight only in infants and did not address the effects of calcium.**

Effects of vitamin D interventions on birth weight were inconclusive.

For growth, a metaanalysis of 17 RCTs **identified for the original report** did not find a significant effect on weight and height gain attributable to calcium supplement in children ranged from 3 to 18 years of age. **The current report did not address pediatric weight or height gain or the effects of calcium alone.**

For **intermediate indices of bone health**, one well-conducted systematic review of RCTs **identified for the original report** found that vitamin D₃ (up to 800 IU/d) plus calcium (approximately 500 mg/d) supplementation 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. **Of the studies identified for the current report, one of seven RCTs of vitamin D supplementation alone and six of seven RCTs of vitamin D plus calcium found increases in BMC/BMD: The study of vitamin D alone that reported a positive effect enrolled infants, whereas the studies of vitamin D and calcium primarily enrolled postmenopausal women; the study that reported no effect of administering both vitamin D and calcium enrolled only men. Thus, the findings from the 2009 report with respect to both vitamin D alone and in combination with calcium relevant to intermediate indices of bone health remain unchanged with the incorporation of newer, relevant data. Findings on clinical outcomes are reported above.**

For clinical outcomes of bone health (fracture risk), a post-hoc analysis of the WHI CaD 7-year data that stratified participants by use of personal vitamin D and calcium supplements at baseline found that among women not taking supplements at baseline, the intervention significantly reduced the risk for hip fracture.

For breast cancer, subgroup analyses in four cohort studies **identified for the original report** consistently found that calcium intake in the range of 780 to 1,750 mg/d in premenopausal women was associated with a decreased risk for breast cancer. In contrast, cohort studies of postmenopausal women are consistent in showing no association of calcium intake with the risk of breast cancer. **Studies of calcium alone were not included in the updated report.**

For prostate cancer, three of four cohort studies **identified for the original report** found significant associations between higher calcium intake (>1,500 or >2,000 mg/day) and increased risk of prostate cancer, compared with men consuming lower amount of calcium (500–1,000 mg/

day). **Studies of calcium alone were not included in the updated report.**

For cardiovascular events, a cohort study and a nested case-control study **identified for the original report** found associations between lower serum 25(OH)D concentrations (less than either about 50 or 75 nmol/L) and increased risk of total cardiovascular events; however, a RCT found no effect of supplementation, and studies of specific cardiovascular events were too sparse to reach conclusions. **For the current report, studies assessing associations between cardiovascular events and serum 25(OH)D concentrations also reported inconsistent results. Thus, the findings from the 2009 report relative to vitamin D remain unchanged with the incorporation of newer, relevant data. One high-quality systematic review that included some of the studies reviewed in the original report and some in the current report found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.**

Taken together, six cohort studies of calcium intake suggest that in populations at relatively increased risk of stroke and with relatively low dietary calcium intake (i.e., in East Asia), lower levels of calcium intake under about 700 mg per day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the United States, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1,000 mg. **Again, studies of calcium alone were not included in the current report.**

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectal, pancreas, prostate, all-cause); incidence of hypertension or specific cardiovascular disease events; immunologic disorders; and pregnancy-related outcomes including preeclampsia were either few in number or reported inconsistent findings. Too few studies of combined vitamin D and calcium supplementation have been conducted to allow adequate conclusions about its possible effects on health. The WHI trial was commonly the only evidence available for a given outcome.

For the current report, we abstracted the methods used to assay serum 25(OH)D for all RCTs included in the assessment of dose-response, as well as the RCTs included in the original report and plotted dose response according to assay method. Although most studies employed radioimmunoassays, some relied on other immunoassay methods, receptor binding assays, and HPLC/tandem mass spectrometry. To characterize the assay methods more completely, we also noted the

country and year in which the assay was performed, when reported, and any information provided on standardization; however, very few studies reported the year assays were conducted or how assays were standardized. Combined with the evidence regarding the significant effect of season of blood draw on serum 25(OH)D concentrations, this lack of information on year of assay renders comparing or combining outcomes challenging, even when the same type of assay was used.

As demonstrated by the findings of a number of trials and post hoc analyses identified for the current report, adherence to interventions in trials also remains a barrier to interpretation of study findings and assessing the true effects of supplementation on health outcomes.

Table A. Findings of the original report compared with the current report

This table summarizes the findings of the 2009 and current reports by study design and compares the findings across reports. “None identified” indicates that no studies were identified for that outcome and study design. “None included” indicates that studies for that outcome or of that design were excluded from the reports. For observational studies, “inverse association” refers to an association between lower serum 25(OH)D concentrations and a higher risk for the outcome of interest; “association” or “positive association” refers to an association between higher serum 25(OH)D concentration and a higher risk for the outcome.

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Bone Health Vitamin D						
Rickets	None identified	None identified	Conclusions based on 2006 Ottawa EPC report showed strong effect	None identified	None identified	No new studies to compare
BMD/BMC	(3 RCTs) No effects of vitamin D supplementation on BMC or BMD	None included	The Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents	(8 RCTs) 1 RCT in infants showed a trend toward a positive effect on BMC; 1 RCT in postmenopausal women showed reduced loss of hip BMD but not spinal; 6 RCTs showed no effect	None included	Both 2009 and newer studies had mixed results
Fracture	(3 RCTs) no effect of vitamin D on total fracture risk	None identified	Conclusions based on 2006 Ottawa EPC report were mixed	None identified	(8 observational studies) 3 studies of hip fracture showed mixed results; 1 showed a significant inverse association. Two studies of total fragility fracture showed mixed results.	Both 2009 and newer studies had mixed results

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Muscle strength/falls	None included	None included	Conclusions based on 2006 Ottawa EPC report were mixed	(2 RCTs on fall risk in elderly) 1 reported no effect; 1 reported effects only in subgroups (2 RCTs on muscle strength) both showed positive effects but one showed effects only in those with lower serum 25(OH)D	(1 prospective cohort on falls) inverse association of 25(OH)D and falls risk (4 prospective cohort studies on muscle strength) ¾ showed inverse association of 25(OH)D with muscle strength	Both original and newer studies had mixed results
Bone Health Vitamin D+Ca						
Rickets	None identified	None identified	None identified	None identified		
BMD/BMC	(3 RCTs) 1 RCT in healthy girls showed no effects on BMC; 2 RCTs in postmenopausal women showed positive effects on BMD	None included	Ottawa EPC report concluded that overall, there is good evidence that vitamin D+Ca resulted in small increases in BMD of the spine, total body, femoral neck, and total hip	(7 RCTs) 2 RCTs in girls and young women showed positive effects; 4 RCTs in post- menopausal women had mixed effects; 1 RCT in men showed no effects	None included	Both original and newer studies had mixed results
Fracture	(1 RCT) Vitamin D+Ca reduced risk of stress fracture among premenopausal women	None identified	Ottawa EPC report concluded that supplementation with vitamin D +calcium is effective in reducing fractures in institutionalized populations	(1 RCT and 1 post-hoc analysis, both rated A) Post-hoc analysis of year-7 WHI data showed significantly decreased risk for hip fracture (but not overall fracture) among women who did not use personal supplements at baseline; 3-year study of postmenopausal women / found no effect on fracture at any site	None identified	General agreement among original Ottawa EPC report, 2009 report, and current report that vitamin D+Ca reduces risk for some fractures but not consistent across fracture types or populations. Post-hoc analysis of WHI data demonstrates need to consider baseline supplement use.

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Muscle strength/falls	(1 RCT) 5-year analysis of WHI subsample found no effect on performance	None included	Ottawa EPC report found evidence that supplemental vitamin D reduces falls in postmenopausal women and effect for older men is inconsistent	(1 RCT on muscle strength/1 RCT on falls) no effects of vitamin D+Ca on muscle strength or fall risk	None identified	2009 report consistent with current report that vitamin D+Ca supplementation does not affect risk for falls or muscle strength but too few studies to draw firm conclusions
Pregnancy-Related Outcomes Vitamin D						
Birth weight/length (infancy)	(7 RCTs) 2 out of 7 studies (from same center) reported significant effect of supplement on birth weight; 5 reported no effects	(2 prospective cohorts) no effects	Diverse populations and methodological approaches precluded conclusions	(5 RCTs) 1 out of 5 reported significant effect of supplement intake on birth weight and length; remaining 4: no effect	(2 prospective cohorts) half observed association of 2nd trimester maternal serum 25(OH)D with birth weight	Only 1 C-rated RCT observed an effect of vitamin D; compliance was a challenge in several RCTs
Small-for gestational age (SGA)	No studies identified	No studies identified	NA	No studies identified	(2 prospective cohort studies) 1 found an inverse association of serum 25(OH)D with risk for SGA; the other found a U-shaped association	Differences in observations between studies
Preterm birth	No studies identified	No studies identified	NA	No studies identified	(1 prospective cohort study and 1 nested case-control) the prospective cohort observed an inverse association with risk, the nested case-control observed no association	Differences in observations among studies

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Preeclampsia	No RCTs identified	(1 nested case-control) study observed an association between serum 25(OH)D <37.5 nmol/L and increased risk for preeclampsia	Studies too small in number to reach conclusions	(2 RCTs (pooled in one article)) vitamin D supplementation (4000IU/d but not 2000IU) reduced the risk for preeclampsia	(7 observational studies (5 nested case-control and 2 prospective cohort)): 5 of 7 studies observed an association between serum 25(OH)D <50nmol/L and increased risk for preeclampsia	Newer studies suggest possible effect of serum 25(OH)D concentration or vitamin D supplementation on reducing risk for preeclampsia
Pregnancy-Related Outcomes Vitamin D+Ca						
Birth weight/length (infancy)	(1 C-rated nonrandomized trial) study found significant effect of vitamin D+Ca supplementation on birth weight	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings
SGA	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preterm birth	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preeclampsia	(1 C-rated RCT) Study found no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) on prevention of preeclampsia	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings
All-Cause Mortality						
All-cause mortality Vitamin D	(1 RCT and reanalysis of existing SR) vitamin D supplementation had no significant effect	(4 cohort studies): 3 reported no association; 1 reported a trend toward an inverse association	No relationship of vitamin D with all-cause mortality	None identified	(25 observational studies) 7 reported no association; 16 reported an inverse association; 2 reported a U-shaped association	Both the 2009 and the current report suggest no relationship of vitamin D with all-cause mortality

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
All-cause mortality Vitamin D+Ca	(reanalysis of existing SR) vitamin D+Ca supplementation had no significant effect	None identified	No relationship of vitamin D+Ca and all-cause mortality	None identified	None identified	No literature on vitamin D+Ca and all-cause mortality
CVD Vitamin D						
Hypertension	None identified	(2 observational studies) 2 large prospective cohort studies observed a significant inverse association of serum 25(OH)D with risk for hypertension	Too few studies to draw conclusions	None identified	(2 observational studies) 1 C-rated prospective cohort study observed an inverse association between serum 25(OH)D and risk for hypertension; 1 A-rated cohort study observed a j-shaped association with risk for hypertension	Relative agreement between 2009 report findings and current report except for observed j-shaped association between serum 25(OH)D and hypertension risk
Blood pressure	(3 RCTs) 3 trials reported no effect of vitamin D on diastolic blood pressure, but diastolic pressure was decreased in 1 study, unchanged in 1, and increased in 1			(10 RCTs) 7 reported no effect, vitamin D decreased blood pressure in 2 studies, and vitamin D increased systolic blood pressure in 1	None included	2009 report and current report agree that effects of vitamin D supplementation on blood pressure are inconsistent, based on small numbers of studies
CVD events	(1 RCT) No effect of vitamin D supplementation on risk for CV events in elderly	(4 cohort studies) 2 studies reported a significant inverse association between serum 25(OH)D and total CV events; 2 studies reported no associations	Mixed effects reported	None identified	(1 SR of prospective studies; 7 new studies) SR found significant inverse association of serum 25(OH)D and CV events; new cohort studies found mixed effects	Associations of serum 25(OH)D with CVD events observed in some cohort studies but not all and not supported by RCTs

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
CVD mortality	(1 RCT) No effect of vitamin D supplementation on risk for CV death in elderly	None included	Too few studies to draw conclusions	None identified	(7 cohort studies, 1 nested case-control) Increased risk for cardiovascular death for those with the lowest serum 25(OH)D concentrations compared with the highest	Mixed findings between 1 RCT in 2009 report and 8 observational studies identified for current report
CVD Vitamin D+Ca						
Hypertension	(1 RCT) The WHI reported no effect of vitamin D+Ca supplementation on hypertension risk	None identified	No effects reported; small number of trials	None identified	None identified	2009 report and current report identified no effects
Blood pressure	(2 RCTs) No effect of supplementation seen on blood pressure at short or long followup times	None included	No effects reported; small number of trials	None identified	None included	2009 report and current report identified no effects
CVD events	(1 RCT) WHI CaD Trial 7-year followup found no effect on any CV outcome, but a trend toward increased risk for a composite cardiovascular outcome with supplementation	None included	No significant effects of Vitamin D+Ca but trend toward increasing risk of CV events with supplementation	(1 post-hoc analysis of the WHI trial) no effect of study supplements (400IU vitamin D ₃ and 1000mg Ca) alone on risk for CV events at >5 years followup	None identified	Post-hoc reanalysis of WHI CaD outcomes by use of personal supplements at baseline finds no effect of study intervention on risk for CVD

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Cancer Vitamin D						
Total cancer/ cancer mortality	(2 RCTs) no effect of vitamin D supplementation on risk for cancer mortality	(1 cohort study) analysis of NHANES III found no association between 25(OH)D status and risk for cancer mortality		No new RCTs identified	(2 cohort studies assessed association with cancer incidence) no association of 25(OH)D and total cancer incidence (10 cohort studies and 1 nested case-control assessed association with total cancer mortality) 5 cohort studies saw no association; 3 cohorts and the nested case-control observed a trend toward an inverse association; 1 observed a trend toward a positive association; 1 observed a U-shaped association	Totally of studies suggest no or complicated association of 25(OH)D status with cancer mortality
Prostate cancer	No studies identified	(12 nested case-control studies) 8 studies found no association between serum 25(OH)D concentrations and prostate cancer risk; 1 study found a significant inverse association between lower baseline serum 25(OH)D concentrations (<30 compared with >55 nmol/L) and higher risk (rated C); another C-rated study observed a U-shaped association (C-rated)	Observational studies only; mixed findings on associations	No studies identified	(7 observational studies) 4 nested case-control studies and 1 cohort found no association of serum 25(OH)D with risk for prostate cancer; 2 nested case-controls observed a trend toward increasing risk with higher serum 25(OH)D concentrations	2009 and current report find observational studies only, with mixed findings on associations

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Breast cancer	No studies identified	(2 observational studies) 2 nested case-controls observed no association of serum 25(OH) status with risk for breast cancer in 7–12 years followup	Two observational studies suggest no association	(1 RCT on breast density) vitamin D intake greater than 400IU/d decreased mammographic density	(8 observational studies) 2 cohort and 4 nested case-control studies found no association; 2 nested case-control studies found increasing risk of breast cancer with decreasing 25(OH)D concentrations	2009 and current report find observational studies only, with mixed findings on associations
Colorectal cancer(CRC)	(1 RCT) no effect of supplements over 5 years followup	(8 observational studies) 2 nested case-control studies and 1 cohort study found inverse associations between 25(OH) D concentrations and risk for CRC; 5 nested case-control studies found no association	Observational studies report mixed associations and RCT shows no effect	No studies identified	(4 observational studies) 3 nested case-control studies identified a trend toward an inverse association of 25(OH)D and CRC risk; 1 nested case-control found no association	2009 and current report identify mixed findings
Pancreatic cancer	No studies identified	(2 observational studies) risk for pancreatic cancer increased with increasing serum 25(OH)D concentrations	Two few studies to draw conclusions	No studies identified	(8 nested case-controls pooled) risk for pancreatic cancer increased among those with 25(OH)D>100 nmol/L compared with <25nmol/L	Observational studies in 2009 and current reports suggest increasing risk for pancreatic cancer with increasing serum 25(OH)D
Cancer Vitamin D+Ca						
Total cancer mortality	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions
Prostate cancer	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Breast cancer	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for breast cancer	No studies identified		(WHI CaD post-hoc analysis) assessment of breast cancer risk among trial participants stratified by use of personal supplements at baseline reported a trend toward decreasing risk among women who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Colorectal cancer (CRC)	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for CRC	No studies identified	Too few studies to draw conclusions about supplementation	(WHI CaD post-hoc analysis) assessment of CRC risk among trial participants stratified by use of personal supplements at baseline reported no difference in risk between personal supplement users and those who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Pancreatic cancer	No studies identified	No studies identified		No studies identified	No studies identified	
Immune Function Vitamin D						
Infectious illnesses	No studies identified	(2 observational studies) NHANES III found no significant association between serum 25(OH)D concentrations and infectious disease mortality		(4 RCTs) 4 RCTs of infants and adults reported no effects	(9 observational studies) 3 cohort studies observed an inverse association of cord blood 25(OH)D and risk for infections at 3–6 months; two cohort studies observed inverse associations among school-age children; 3 cohort studies of adults observed similar associations with various infectious illnesses	Number of studies in 2009 report too small to assess association of serum 25(OH)D with risk for infection; current report identified RCTs and observational studies, but no consistent effects or associations emerged

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Autoimmune disorders	No studies identified	No studies identified	No studies on which to base conclusions	(1 RCT) a subgroup analysis of WHI CaD participants found no effect of supplementation on risk for rheumatoid arthritis	(4 observational studies) 3 nested case-control studies and 1 cohort study reported mixed associations of serum 25(OH)D concentrations with risk for type 1 diabetes; 1 study reported mixed associations of serum 25(OH)D with risk for multiple sclerosis	No studies in 2009 report on association of serum 25(OH)D with risk for autoimmune diseases; current report identified 1 RCT and observational studies, but no consistent effects or associations emerged
Asthma, Wheeze, Atopy		(1 observational study) a cohort study suggested an association of maternal 25(OH)D concentration and increased risk for eczema in their children but did not assess children's serum 25(OH)D	Too few studies on which to base conclusions	(1 RCT) no effect of prenatal supplementation on risk for wheeze, atopy, or eczema	(5 observational studies) mixed associations seen in cohorts of children between serum 25(OH)D status and risk for atopy, eczema, wheeze, and asthma	Number of studies in 2009 report too small to assess association of serum 25(OH)D with risk for asthma, atopy, or wheeze; current report identified 1 RCT and 5 observational studies, but no consistent effects or associations emerged
Immune Function Vitamin D+Ca						
	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies identified in 2009 or current report on which to base conclusions
Adverse events						
Nephrolithiasis	(WHI CaD Trial) trial reported increased risk for nephrolithiasis among supplement users			(2 RCTs) no incidents of nephrolithiasis were reported in studies that administered 1100 and 2000IU/d vitamin D		Observation of increased risk for nephrolithiasis in original WHI study; very small number of RCTs identified for current report did not support this finding

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Other Adverse Events	47 of 63 RCTs included no information on adverse events; no serious AEs were reported			41 of 55 RCTs included no information on adverse events; 1 RCT reported that no adverse events were reported; of 9 studies that assessed hypercalcemia, 1 RCT that administered 1000IU vitamin D and 1000mg Ca reported 1 case		Few studies in the 2009 or the current report reported AEs; consistent finding of new serious AEs
Dose-Response for Vitamin D	(26 RCTs) serum 25(OH)D increased with increasing dosages, but trajectories varied widely by age group, baseline serum 25(OH)D, and duration	Not included		(1 systematic review and 19 RCTs of vitamin D ₃ with or without calcium) serum 25(OH)D increased with increasing dosages but trajectories varied widely by age group, baseline serum 25(OH)D, duration, and assay. Too few new studies included Ca to assess effect.	Not included	Observations based on new studies agree with those of 2009 report; current report also stratified dose-response by assay type. Patterns appear to differ slightly but too few studies to ascertain.

25(OH)D = 25-hydroxyvitamin D; AEs = Adverse Events; BMD = Bone mineral density; BMC = Bone mineral content; Ca = Calcium; CaD = Calcium/Vitamin D; CRC = Colorectal Cancer; CVD = Cardiovascular Disease; EPC = Evidence-based Practice Center; IU = International Unit; NHANES III = National Health and Nutrition Examination Survey; RCT = Randomized controlled trial; SGA = Small for gestational age; WHI = Women's Health Initiative

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Full Report

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