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Vitamin D and Calcium: A Systematic Review of Health Outcomes

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Preface

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 Office of Dietary Supplements/National Institutes of Health, the Public Health Agency of Canada, Health Canada, and Food and Drug Administration requested and provided funding for this report. 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.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

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.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to **epc@ahrq.gov.**

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Structured Abstract

Background: Since the 1997 Dietary Reference Intake (DRI) values for vitamin D and calcium were established new data have become available on their relationship, both individually and combined, to a wide range of health outcomes. The Institute of Medicine/Food and Nutrition Board has constituted a DRI committee to undertake a review of the evidence and potential revision of the current DRI values for these nutrients. To support this review, several US and Canadian federal government agencies commissioned a systematic review of the scientific literature for use during the deliberations by the committee. The intent of providing a systematic review to the committee is to support transparency of the literature review process and provide a foundation for subsequent reviews of the nutrients.

Purpose: To systematically summarize the evidence on the relationship between vitamin D, calcium, and a combination of both nutrients on a wide range of health outcomes as identified by the IOM, AHRQ and technical expert panel convened to support the project.

Data sources: MEDLINE; Cochrane Central; Cochrane Database of Systematic Reviews; and the Health Technology Assessments; search limited to English-language articles in humans.

Study selection: Primary interventional or observational studies that reported outcomes of interest in human subjects in relation to vitamin D and/or calcium, as well as systematic reviews that met the inclusion and exclusion criteria. Cross sectional and retrospective case-control studies were excluded.

Data extraction: A standardized protocol with predefined criteria was used to extract details on study design, interventions, outcomes, and study quality.

Data synthesis: We summarized 165 primary articles and 11 systematic reviews that incorporated over 200 additional primary articles. Available evidence focused mainly on bone health, cardiovascular diseases or cancer outcomes. For many outcomes, it was difficult to draw firm conclusions on the basis of the available literature concerning the association of either serum 25(OH)D concentration or calcium intake, or the combination of both nutrients. Findings were inconsistent across studies for colorectal and prostate cancer, and pregnancy-related outcomes including preeclampsia. There were few studies for pancreatic cancer and immune function. Among trials of hypertensive adults, calcium supplementation lowered systolic, but not diastolic, blood pressure by 2-4 mm Hg. For body weight, the trials were consistent in finding no significant effect of increased calcium intake on weight. For growth rates, a meta-analysis did not find a significant effect on weight or height gain attributable to calcium supplement in children. For bone health, one systematic review found that vitamin D plus calcium supplementation resulted in small increases in BMD of the spine and other areas in postmenopausal women. For breast cancer, calcium intakes in premenopausal women were associated with a decreased risk. For prostate cancer, some studies reported that high calcium intakes were associated with an increased risk.

Limitations: Studies on vitamin D and calcium were not specifically targeted at life stages (except for pregnant and postmenopausal women) specified for the determination of DRI. There

is large variation on the methodological quality of studies examined. Use of existing systematic reviews limits analyses that could be performed on this source of information.

Conclusions: The majority of the findings concerning vitamin D, calcium, or a combination of both nutrients on the different health outcomes were inconsistent. Synthesizing a dose-response relation between intake of either vitamin D, calcium or both nutrients and health outcomes in this heterogeneous body of literature prove challenging.

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Executive Summary

Background

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 is 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's (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 US and Canadian government scientists 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 lifestage groups, reports on potential adverse effects, dose-response relations between intakes and circulating 25-hydroxyvitamin D [25(OH)D] concentrations and between 25(OH)D concentrations and several health outcomes.

This report includes a systematic review of health outcomes relating to vitamin D and calcium intakes, both alone and in combination. The executive summary is provides a high-level overview of the findings of the systematic review. Recommendations and potential revisions of nutrient reference values (ie, 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 answered key scientific questions on how dietary vitamin D and calcium intake effect 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 the AHRQ's *Methods Guide for Comparative Effectiveness Reviews*. The report will be provided to an IOM committee charged with updating vitamin D and calcium DRIs. This report does not make 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 this report are as follows:

Key Question 1. What is the effect of vitamin D, calcium, 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?

Key Question 2. What is the effect of vitamin D, calcium 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 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?

We 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.

We rated the primary studies using a three-grade system (A, B, C), evaluating each type of study design (i.e., randomized controlled trial [RCT], cohort, 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 not sufficient to invalidate the results. Grade C studies have significant bias that may invalidate the results.

Results

We 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.

Vitamin D

Vitamin D and growth.

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 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 D_3 (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.

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 B, two 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.

We identified 2 B-rated RCTs and an analysis of the NHANES database (2 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 (~1500 mg/d or 100,000 IU every 4 months). Analyses of Third National Health and Nutrition Examination Survey (NHANES III) showed no significant association between baseline serum 25(OH)D concentrations and total cancer mortality.

Prostate cancer.

Twelve nested case-control studies (three B, nine C) evaluated the association of baseline serum 25(OH)D concentrations and prostate cancer risk. We identified no eligible RCTs. Eight 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 to >55 nmol/L) and higher risk of prostate cancer. Another C-rated study suggested the possibility of an 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 to that of the in between reference level).

Colorectal cancer.

We identified one B-rated RCT, one B-rated cohort study, and seven nested case-control studies (five 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 D_3 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 to 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.

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.

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 >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 pre- or postmenopausal women.

Pancreatic cancer.

Two A-rated nested case-control studies evaluated the association of serum 25(OH)D concentrations and pancreatic cancer. We identified no relevant RCTs. 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 to lower (<49.3 nmol/L) only in those living in low residential UVB exposure areas.

Vitamin D and immunologic outcomes.

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

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.

We 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.

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 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 >70 years.

Bone mineral density (BMD) or bone mineral content (BMC).

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. Consistently with the findings of RCTs in the Ottawa EPC report, the three additional RCTs (one A, one B, one C) that showed no significant effects of vitamin D supplementation on BMC in children or BMD in adults.

Vitamin D and all-cause mortality.

An existing systematic review and meta-analysis of RCTs on vitamin D supplementation for mortality was updated and reanalyzed. We identified one additional C rated RCT. Four additional cohort studies (one 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 all studies, mean age was >70 years and dosages ranged between 400 to 880 IU/d. 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, >23 nmol/L in men and >19 nmol/L in women.

Vitamin D and hypertension and blood pressure.

Hypertension.

We identified no relevant RCTs. In a B-rated combined analysis of the Health Professionals Follow-up Study (HPFS) and the Nurses Health Study (NHS), 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 <37.5 nmol/L, compared to those with higher 25(OH)D concentrations. At 8 years, a similar significant association was found for men, but not for women.

Blood pressure.

We evaluated only RCTs for changes in blood pressure. Three RCTs of vitamin D versus placebo (one 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.

Calcium

Calcium and growth.

One systematic review of RCTs, two additional RCTs (both rated B) and a cohort study (rated C) evaluated calcium supplementation (300-1200 mg/d) and growth in infants and children. In children and adolescents (aged 3–18 y), the systematic review with meta-analysis of 17 RCTs found no significant effect on weight and height gain attributable to calcium supplementation. The summary net difference (weighted mean difference) was 0.14 kg lower weight gain (95% CI -0.28, 0.57) and 0.22 cm lower height gain (95% CI -0.30, 0.74) in those who received supplemental calcium compared to those who did not. There was no evidence for heterogeneity in these analyses. The three primary studies reported similar findings.

Calcium and cardiovascular events.

Ten longitudinal cohort studies and one nested case-control study analyzed associations with various specific cardiovascular events. We identified no eligible RCTs. Most studies were rated A. Notably, the ranges of calcium intake within studied populations varied widely across cohorts. The average intake in the highest quartile (~750 mg/day) in Japanese studies (at one extreme) was less than the average in the lowest quintile (~875 mg/day) in Finnish studies (at the other extreme).

Cardiac events, combined cardiovascular events, and cardiovascular mortality.

Among studies that evaluated the specific cardiovascular outcomes, no significant (or consistent) associations were found between calcium intake and cardiovascular death, combined fatal and nonfatal cardiac events, cardiac death, nonfatal myocardial infarction, or fatal strokes. Among four studies, only the Iowa Women's Health Study (WHS) found a significant association between calcium intake <696 mg/day and higher risk of ischemic heart disease death in white women aged 55-69 years.

Stroke.

The five studies that evaluated total stroke had disparate findings. In two Asian studies (with overall low calcium intake and high risk of stroke compared to Americans), over 11-13 years, people in higher quintiles of calcium intake had progressively lower risks of stroke. A small 10 year Finnish study (with overall high calcium intake compared to Americans) found no association. The two studies that evaluated men alone reported nonsignificant trends in opposite directions. In women, the NHS found a nonsignificant association between calcium intake and stroke after 14 years of followup, but significantly higher stroke risk in those with calcium intake <~500 mg/day compared with women in the next two higher quintiles.

Calcium and body weight.

No study evaluated the incidence of overweight or obesity. We evaluated only RCTs for changes in body weight. We identified three systematic reviews that evaluated RCTs of calcium intake and changes in body weight. Eight additional trials (one A, four B, three C) not identified by these systematic reviews met eligibility criteria; altogether, 49 trials have been identified. Only one of the systematic reviews separately analyzed studies of people on isocaloric diets (where weight loss was not a goal) and studies of people on energy-restricted diets. Overall, 24 included trials investigated calcium supplementation and 15 investigated high dairy diets; 29 trials had energy-neutral background diets and 13 evaluated calcium supplementation in the setting of an energy-restricted (weight loss) diets. Although there was not complete agreement among the systematic reviews, overall, the trials in the systematic review do not support an effect of calcium supplementation on body weight loss. No systematic review analyzed effects of calcium supplementation and body weight change based on life stage or calcium dose. The additional trials found in the update did not alter these conclusions.

Calcium and cancer.

Total cancer.

One RCT (rated B) and one cohort study (rated C) evaluated the relationship between calcium supplementation and total cancer incidence or mortality. The RCT reported a near significant beneficial effect of calcium supplementation (1400-1500 mg/d) on cancer incidence and mortality at 4 years. The cohort study found no association between increasing calcium intakes and cancer incidence or mortality or incidence.

Colorectal cancer.

We identified one systematic review of two RCTs, 19 cohort studies (5 B, 14 rated C), and one B-rated nested case-control study. The systematic review of two RCTs that evaluated high risk populations found no significant difference in colorectal cancer incidence between supplemental calcium and no supplementation. The five B-rated cohort studies and the nested case-control study generally suggested a relationship between increased total calcium intake and reduced colorectal cancer risk, though in only two cohort studies were the associations statistically significant. Among 14 C-rated cohort studies, lower total calcium intake was significantly associated with higher risk of colorectal cancer (5 studies), colon cancer (2 studies), and rectal cancer (2 studies). Followup was 1.4-11.3 years and no study included participants <45 years.

Colorectal polyps.

We identified one systematic review of two RCTs, one B-rated long-term followup of a RCT, one C-rated nonrandomized trial, and four B-rated cohort studies. The systematic review evaluated two trials that tested either 1200 or 2000 mg/d calcium supplementation and found a reduction in the risk of colorectal polyps with calcium supplementation (summary OR = 0.74 [95% CI 0.58, 0.95]). The nonrandomized studies generally suggested a relationship between increased total calcium intake and reduced colorectal polyp risk, though in only two were the associations statistically significant.

Prostate cancer.

Four A-rated cohort studies reported on the association between total calcium intake and the risk of prostate cancer. We identified no additional RCTs. Three of the four studies found significant associations between higher calcium intake (>1500 or >2000 mg/day) and increased risk of prostate cancer, compared to men consuming lower amount of calcium (500-1000 mg/day).

Breast cancer.

Six cohort studies (five B, one C) compared calcium intake and the risk of breast cancer. Subgroup analyses from the four cohort studies consistently found that premenopausal women with calcium intakes in the range 780-1750 mg/day were associated with a decreased risk of breast cancer. No consistent association was found for postmenopausal women.

Breast mammographic density.

One B-rated cohort study found no association between calcium intake and breast mammographic density in premenopausal and postmenopausal women.

Pancreatic cancer.

Two studies (one A, one B) that analyzed three cohorts found no significant association between calcium intake and risk of pancreatic cancer.

Calcium and preeclampsia, hypertension in pregnancy, preterm birth or small infant for gestational age.

Preeclampsia.

A systematic review of twelve RCTs (N = 15,528) of calcium supplementation (≥1000 mg/d) vs. placebo and two cohort studies (one of which was a reanalysis of one of the twelve RCTs) tested the association between calcium intake and preventing preeclampsia in pregnant women. The random effects model meta-analysis of the 12 RCTs found that calcium supplementation reduced the risk of preeclampsia (RR=0.48, 95% CI 0.33, 0.69), albeit with substantial between-study heterogeneity. Notably, more than 80 percent of the randomized women (N=12,914) were in two large trials that together found no significant effect of calcium supplementation for preventing preeclampsia (RR=0.95, 95% CI 0.89, 1.05). There is no obvious explanation for the observed between-study heterogeneity in the aforementioned meta-analysis. The heterogeneity stems from differences in the effects between smaller trials (claiming protective effects) and large trials (showing no effect). The two cohort studies did not find a significant association between calcium intake during the first or second trimester and preeclampsia.

High blood pressure with or without proteinuria during pregnancy.

The same systematic review evaluated calcium for preventing hypertension during pregnancy, with or without proteinuria. Overall, the meta-analysis of 11 RCTs found a significant effect of calcium supplementation RR = 0.70 (95% CI 0.57, 0.86) for the treatment of hypertension during pregnancy, with or without proteinuria. However, there was substantial between-study heterogeneity. Similar to the meta-analysis of preeclampsia, the two largest trials found no significant effect of calcium supplementation and prevention of pregnancy-related hypertension.

Preterm birth.

The same systematic review evaluated preterm births and found no significant effect of calcium supplementation among 10 RCTs (N=14,751). The summary RR was 0.81 (95% CI 0.64, 1.03), but was statistically heterogeneous.

Small for gestational age infant.

The same systematic review evaluated infant size and found no overall significant effects of calcium supplementation among three RCTs (N=13,091). The summary RR was 1.10 (95% CI 0.38, 1.37), without evidence for between-study heterogeneity.

Calcium and all-cause mortality.

One B-rated cohort study found no association between calcium intake and all-cause mortality in men and women aged 40-65 years.

Calcium and hypertension and blood pressure.

Hypertension.

The association between calcium intake and risk of hypertension has been analyzed in five cohort studies (6 articles; one A, one B, four C). The majority of the studies found no association between calcium intake and incidence of hypertension over 2 to 14 years of followup. However, in two studies, subgroup analyses found that in people <40 or <50 years, those in the lowest category of calcium intake (not defined in one study and <500 mg/d in the other) were at significantly higher risk of hypertension than those in higher intake categories (>1100 mg/d in one study). Only the Iowa WHS of postmenopausal women found a significant overall association between calcium intake and incidence of hypertension, such that after 10 years, women in the lowest calcium intake quintile (189-557 mg/d) had significantly higher rates of hypertension than women in all quintiles with intakes >679 mg/d.

Blood pressure.

We evaluated only RCTs for changes in blood pressure. The large majority of the trials of blood pressure have been summarized in six systematic reviews of calcium intake and blood pressure. Overall, across 69 trials of calcium intake and blood pressure, a wide range of calcium supplement doses or total dietary calcium intakes were tested (~400-2000 mg/d, with most testing calcium supplementation of 1000 mg). The large majority of the evidence is most applicable to people aged ~40-70 years. Although not all the systematic reviews separated trials of normotensive and hypertensive participants, the evidence suggests different effects of calcium in these two populations. In general, among trials of hypertensive adults, calcium supplementation lowered systolic blood pressure by a statistically significant 2-4 mm Hg compared to no supplementation. The evidence suggested no significant effect on diastolic blood pressure. In contrast, the trials of normotensive individuals found no significant effect of calcium supplementation on systolic or diastolic blood pressure. The analyses of age, sex, calcium dose, background dietary calcium, supplement versus dietary source, and other factors found no significant associations (or differences).

Combined Vitamin D and Calcium

Combined vitamin D and calcium and growth.

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.

A variety of cardiovascular events after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) 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 non-significant 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.

Combined vitamin D and calcium and body weight.

No studies evaluated the risk of obesity or overweight. We evaluated only RCTs for changes in body weight. We identified 2 RCTs (rated B and C) evaluating 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/d and calcium carbonate (1000 mg/d or 1200 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.

Two RCTs (rated B and C) 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 1000 mg/d) showed no effects while the B-rated trial (vitamin D 1000 IU/d and calcium 1400-1500 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 evaluated colorectal cancer. It reported no significant reduction in colorectal cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) compared to placebo.

Colorectal polyps.

The B-rated WHI trial was the only trial of combined vitamin D_3 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 to 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 to placebo.

Combined vitamin D and calcium and preeclampsia, hypertension in pregnancy, preterm birth or small infant for gestational age.

Preeclampsia.

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.

The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) 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 (1000 mg/d) supplementation or placebo. One RCT of premenopausal women (aged 17-35 years) found that, compared to placebo, vitamin D (800 IU/d) in combination calcium (2000 mg/d) supplementation reduced the risk of stress fracture from military training compared to placebo.

Bone mineral density or bone mineral content.

The Ottawa EPC report concluded that overall, there is good evidence that combined vitamin D_3 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 D_3 (<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, we included only RCTs for our update literature review. We identified three new RCTs (two B, one C) that evaluated BMD outcomes. Two of the trials showed significant improvement in BMD in postmenopausal women receiving vitamin D_2 (300 IU/d) or D_3 (1200 IU/d) plus calcium (1200 mg/d) compared to placebo.

One C-rated RCT evaluated BMC outcomes in healthy girls (aged 10-12 years). Compared to placebo, there was no significant effect of supplementation with vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) on BMC changes.

Combined vitamin D and calcium and all-cause mortality.

An existing systematic review and meta-analysis of 18 RCTs on vitamin D supplementation for mortality was reanalyzed. We identified no additional RCTs. Eleven RCTs (N=44,688) of combined vitamin D (300-800 IU/d) and calcium (500-1200 mg/d) supplementation met inclusion criteria for our reanalysis. The meta-analysis 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 8 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.

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. We evaluated only RCTs for changes in blood pressure. Two trials (one B, one C) tested combined vitamin D (400 IU/d) and calcium (1000 or 1200 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,* and on our updated literature review of studies published after its completion.

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 D_3 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 D_3 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 status ($\leq$40 vs. >40 nmol/L) at baseline, and depending on duration of supplementation ($\leq$3 vs. >3 months).

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.

The WHI trial (vitamin D_3 400 IU in combination with 1000 mg calcium carbonate versus 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.

Adverse events reported in RCTs.

The 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 this report, 47 did not report information on adverse events. Five 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 5714 IU/d vitamin D_3 or ranged from 5000 to 10,000 vitamin D_2) and/or calcium supplementations (doses ranged from 200 to 1500 mg/d) reported few cases of gastrointestinal disruption such as constipation, diarrhea, upset stomach, musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, renal calculi and craniotabes. However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study.

Summation

This 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 TEP. 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, among RCTs of hypertensive adults, calcium supplementation (400-2000 mg/d) lowered systolic, but not diastolic, blood pressure by a small but statistically significant amount (2-4 mm Hg).

For body weight, despite a wide range of calcium intakes (from supplements or from dairy and nondairy sources) across the calcium trials, the RCTs were fairly consistent in finding no significant effect of increased calcium intake on body weight.

For growth, a meta-analysis of 17 RCTs 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.

For bone health, one well-conducted systematic review of RCTs found that vitamin D_3 (up to 800 IU/d) plus calcium (~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.

For breast cancer, subgroup analyses in four cohort studies consistently found that calcium intake in the range of 780 to 1750 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.

For prostate cancer, three of four cohort studies found significant associations between higher calcium intake (>1500 or >2000 mg/day) and increased risk of prostate cancer, compared to men consuming lower amount of calcium (500-1000 mg/day).

For cardiovascular events, a cohort study and a nested case-control study 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. 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/day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the US, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1000 mg.

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectum, 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.

Evidence Report

Chapter 1. Introduction

Background

The Food and Nutrition Board of the Institute of Medicine (IOM), with funding from agencies and departments of the US and Canadian governments, recently completed their 10-year development of nutrient reference values entitled Dietary Reference Intakes (DRI).[1] In September, 2007, the IOM held a conference to examine the lessons learned and future challenges from the process used to develop the DRI values.[2] One improvement identified at that meeting for DRI updating was the use of systematic reviews to enhance the transparency and rigor of the literature review process that is a necessary component in the deliberations of DRI committees. To assess the feasibility of implementing this approach in the DRI updating process, the Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH) through the Agency for Healthcare Research and Quality (AHRQ) requested the Tufts Medical Center Evidence-based Practice Center (Tufts-EPC) perform an exercise to identify the issues and challenges of conducing systematic reviews as a component of the process used to support the development and updating of DRI values. The Tufts-EPC assembled a group of nutrition experts from academic institutions and federal government agencies, led participants in teleconferences and meetings, and conducted exercises in formulating questions that would be amenable to a systematic review of the scientific literature and abstract screening.[3] One of the intents of this exercise was to identify limitations, challenges, and unanticipated issues that IOM committees may face prior to actually initiating the use systematic reviews as a routine part of the DRI process.

Following these activities, a working group of US and Canadian government scientists convened to determine whether the scientific literature was sufficient to justify a new review of the vitamin D DRI. To address this issue in May and September of 2007, two conferences were held on the topic of vitamin D and health.[4] As a result of these conferences in March of 2008 the IOM convened a working group of US and Canadian government scientists to determine whether significant new and relevant scientific evidence had become available since the 1997 IOM publication of vitamin D DRI to justify initiating a formal review and potential revision of the values.[5] The working group reviewed the proceedings of the two conferences and the results from a systematic review commissioned by the ODS on the effectiveness and safety of vitamin D in relation to bone health conducted by the University of Ottawa EPC (Ottawa-EPC).[6] They concluded that there was sufficient new data on bone health for several of the lifestage groups, on potential adverse effects, and on dose-response relationships between intakes and circulating 25-hydroxyvitamin D [25(OH)D] concentrations, and between 25(OH)D concentrations and several health outcomes to warrant a formal review and potential revision of the values.[5] As a result, the NIH/ODS, Public Health Agency of Canada, Health Canada and FDA commissioned the Tufts-EPC to update the Ottawa-EPC report, and systematically review the data related to vitamin D and calcium with respect to a broader spectrum of health outcomes.

Sources, Metabolism and Functions of Vitamin D

Vitamin D was classified as a vitamin in the early 20th century and in the second half of the 20th century as a prohormone ("conditional" vitamin).[7,8] There are two forms of vitamin D, vitamin D_3 (cholecalciferol), which is produced from the conversion of 7-dehydrocholesterol in

the epidermis and dermis in humans, and vitamin D_2 (ergocalciferol) which is produced in mushrooms and yeast. The chemical difference between vitamin D_2 and D_3 is in the side chain; in contrast to vitamin D_3, vitamin D_2 has a double bond between carbons 22 and 23 and a methyl group on carbon 24.

The major source of vitamin D for humans is exposure to sunlight. The efficiency of the conversion of 7-dehydrocholesterol to vitamin D_3 is dependent on time of day, season of the year, latitude, skin color and age. There is little vitamin D that occurs naturally in the food supply. The major naturally occurring food sources include fatty fish, beef liver and egg yolk. In the U.S. and Canada, the major dietary source of dietary vitamin D is fortified foods, including cow's milk and, depending on country, other fortified foods and dietary supplements. These sources cannot be relied on in countries other than the U.S. and Canada. Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein.

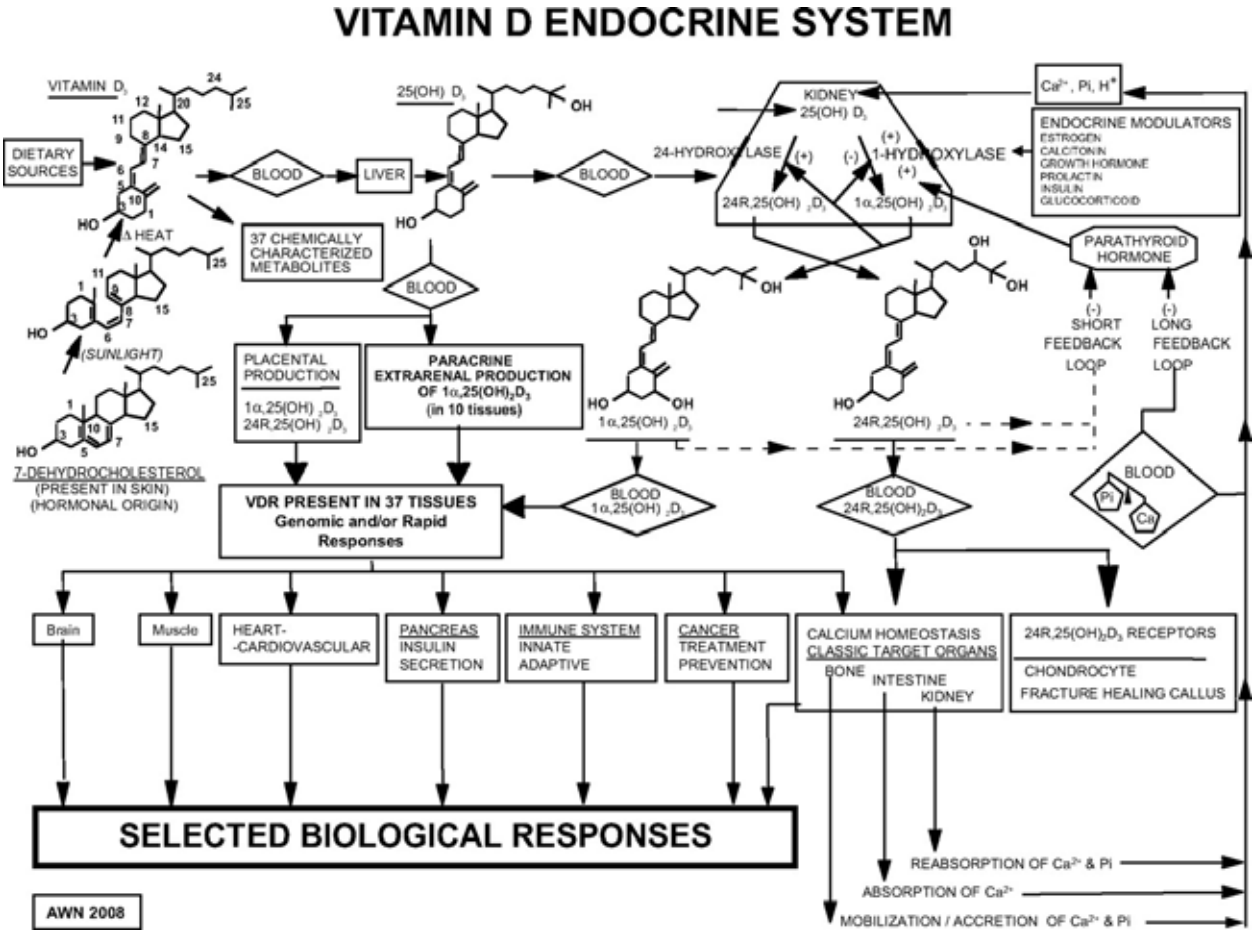
In its native form vitamin D is not biologically active, the active form is $1,25(OH)_2D$. The conversion of vitamin D to $1,25(OH)_2D$ requires two hydroxylation in tandem. Vitamin D is first hydroxylated by the liver to form 25(OH)D, which is then hydroxylated by the kidney to form $1,25(OH)_2D$. 25(OH)D has low biological activity, but it is the major form of vitamin D that circulates in the blood stream. Serum 25(OH)D concentrations are generally thought to reflect nutritional status.[7,8] When adequate amounts of vitamin D are available, the kidney, the major site of $1,25(OH)_2D$ production converts some of the 25(OH)D to alternate hydroxylated metabolites, which have low biological activity (e.g., $24,25(OH)_2D$ or $1,24,25(OH)_3D$). Renal synthesis of $1,25(OH)_2D$ is tightly regulated by plasma parathyroid hormone, together with serum calcium and phosphorus concentrations. Additional tissues that express the enzyme that catalyses the conversion of 25(OH)D to $1,25(OH)_2D$, 25-hydroxyvitamin D3-1-α-hydroxylase, include colon, prostate, mammary gland, macrophages, antigen-presenting cells, osteoblasts and keratinocytes.[9]

Vitamin D has both genomic and nongenomic functions. For the genomic functions, $1,25(OH)_2D$ interacts with nuclear vitamin D receptors to influence gene transcription. Nuclear receptors for $1,25(OH)_2D$ have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle and skin. For the nongenomic functions, $1,25(OH)_2D$ acts like a steroid hormone, working through activation of signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle.

One of the major biological functions of vitamin D is to maintain calcium homeostasis which impacts on cellular metabolic processes and neuromuscular functions. Vitamin D affects intestinal calcium absorption by increasing the expression of the epithelial calcium channel protein, which in turn enhances the transport of calcium through the cytosol and across the basolateral membrane of the enterocyte. Vitamin D also facilitates the absorption of intestinal phosphate. $1,25(OH)_2D$ indirectly affects bone mineralization by maintaining plasma calcium and phosphorus concentrations, and subsequently extracellular calcium and phosphorus concentrations at the supersaturating range necessary for mineralization. $1,25(OH)_2D$, in concert with parathyroid hormone, also causes demineralization of bone when calcium concentrations fall to maintain plasma concentrations within a narrow range. It has yet to be determined whether $1,25(OH)_2D$ directly influences bone mineralization.

In addition to intestine and bone, a wide range of other tissues and cells that are influenced by vitamin D. Five biological systems have vitamin D receptors and are responsive to $1,25(OH)_2D$, as summarized in Figure 1.[10] These systems include immune, pancreas, cardiovascular, muscle and brain; and control of cell cycle. The biological effects of $1,25(OH)_2D$ are diverse. For example, as recently noted, $1,25(OH)_2D$ inhibits PTH secretion and promotes insulin secretion, inhibits adaptive immunity and promotes innate immunity, and inhibits cell proliferation and stimulates their differentiation.[11] A number of recent reviews have appeared on these topics.[10-17]

Figure 1. Summary of the vitamin D endocrine system



From Norman AW. A vitamin D nutritional cornucopia: new insights concerning the serum 25-hydroxyvitamin D status of the US population.[10]

Sources, Metabolism, and Functions of Calcium

The major source of dietary calcium in the North American diet, but not necessarily other counties, is dairy products (about 70 percent). Additional sources include commercial white bread made with calcium sulfate, foods made with milk products, leafy greens, canned fish and calcium fortified foods. Oxalic acid impedes the absorption of calcium from many plant foods. Intestinal calcium absorption is regulated by two processes. One route of intestinal calcium

absorption is dependent on $1,25(OH)_2D$. This process occurs primarily in the duodenum and proximal jejunum, is saturable, is energy dependent, and involves a calcium binding protein. The $1,25(OH)_2D$-dependent absorption of calcium is stimulated by low dietary calcium intakes. The other route of intestinal calcium absorption is independent of $1,25(OH)_2D$ and is termed paracellular. This process is passive (does not depend on carrier proteins or energy) and occurs primarily in the jejunum and ileum. Calcium is absorbed between cells, rather than through cells, and down the concentration gradient. Calcium can be transported in blood bound to albumin and prealbumin, complexed with sulfate, phosphate or citrate, or in a free (ionized) state.

Calcium is transported in blood bound to proteins (~40 percent), primarily albumin and prealbumin, complexed with sulfate, phosphate or citrate (~10 percent), and in the ionized form (~50 percent). Blood calcium concentrations are controlled extracellularly by parathyroid hormone, calcitriol and calcitonin. Intracellular calcium concentrations are maintained at relatively low levels. Increased intracellular calcium concentrations occur in response to second messengers by stimulating release from intracellular sites (endoplasmic reticulum, mitochondria) and hormones by facilitating influx from extracellular sites by transmembrane diffusion or channels.

Calcium balance measures provide information on calcium absorption relative to calcium loss in urine, sweat and endogenous intestinal secretions. During periods of growth, positive calcium balance implies bone mineralization but does not provide an indication of whether the rate of bone mineralization is optimal. During adulthood negative calcium balance implies calcium lost from bone but does not provide an indication of which site(s). Calcium balances measures provide an indication of current but not prior calcium balance. An alternate approach to assessing bone mineralization is by measuring bone mineral density.

Approximately 99 percent of the calcium in the human body is in bone and teeth. In addition to structural roles, calcium has other critical functions. These include serving as a second messenger (e.g., cytosolic calcium, calcium-dependent trigger proteins, removal of calcium stimulus) and protein activator (e.g. phospholipase A_2, calpains [calcium dependent proteins that contain calmodulin-like domains], blood clotting enzymes, annexins [calcium and phospholipid binding proteins]). $1,25(OH)_2D$ plays a critical role in regulating plasma calcium concentrations through its role in intestinal calcium absorption, bone resorption and renal calcium resorption. These functions of calcium are frequently classified into the following general categories; bone development and maintenance, blood clotting, transmission of nerve impulses to target cells, muscle contraction and cell metabolism. In addition, calcium may play a role in colon cancer, kidney stones, blood pressure, body weight and lead absorption.

Challenges for the DRI Committees

The following generic challenges must be addressed, preferably in a standardized way, before additional systematic reviews are conducted for use by upcoming DRI committees to ensure the resulting product will yield a maximally useful document.[3] Because the potential volume of peer reviewed literature on the biological effects of most essential nutrients is large and continues to grow, rational and well defined eligibility criteria will need to be identified by the committee to manage the workload. Appropriate questions must be formulated so that the answers to those questions can be used to inform the DRI development process, ensure transparency and reproducibility, and serve as the foundation for future updates as new data emerge. Experience has shown that in the absence of unlimited resources, only a limited set of

questions can be addressed. Hence, it is critical that the committee prioritize the topics and refine the questions in a way that will address critical issues for development and revision of DRI values.

Age specific intermediate or surrogate outcomes will need to be identified by the committee when few or no studies directly link specific nutrient intakes with clinical outcomes. Preferably, these would include only validated surrogates of the clinical outcome, that is outcomes that are strongly correlated with the clinical outcome (e.g., bone mineral density as a surrogate for fractures in postmenopausal women), and changes in their status reflect corresponding changes in the risk of the clinical outcome (e.g., changes in bone mineral density reflect changes in fracture risk in postmenopausal women).[18] In the absence of validated surrogate outcomes, intermediate outcomes must be identified and considered (e.g., absence of anemia as an intermediate outcome for the absence of disease or serum osteocalcin [bone turnover index] as an intermediate marker for fractures). When a nonvalidated intermediate outcome must be considered, the implicit assumption is that they would have the properties of a validated surrogate outcome. Not only should this assumption be made explicit, but the uncertainties involved in applying this assumption should be identified, documented, and discussed by the committee.

Reliable indicators of exposure (or biomarkers) need to be identified by the panel. A reliable biomarker should accurately reflect the degree of biological exposure to the nutrient of interest and fulfill the classic risk assessment model (e.g., exhibit a dose-response relationship). To that extent, the measurement of biological exposure should be independent and free from any interaction with the self-estimated intake of the nutrient of interest. It is important for the DRI committee to recognize that use of a biomarker to evaluate the strength of downstream associations requires that the biomarker concentrations be back translated into levels of nutrient intake and that if an association is found between a given biomarker concentration and risk of a clinical outcome, an estimate of the nutrient intake that corresponds to the clinical outcome will likewise be necessary.

Additional challenges for the DRI committees with respect to the conduct of systematic review include defining relevance of studied populations with respect to nutrient distributions and health risks to those for which reference values are being established, generalizability of well-controlled experiments with few subjects, generalizability of studies of subjects having narrow eligibility criteria, applicability for findings of animal studies to humans when data in humans are nonexistent, generalizability of early studies that used methodologies not considered state of the art or directly comparable with contemporary methods (e.g., change in analytical techniques or standardization), appropriate approaches to evaluating, interpreting and integrating data from observational studies with interventional data, and approaches to factor contemporary issues into the process, such as the role of genomics and nutrient fortification into the systematic review.

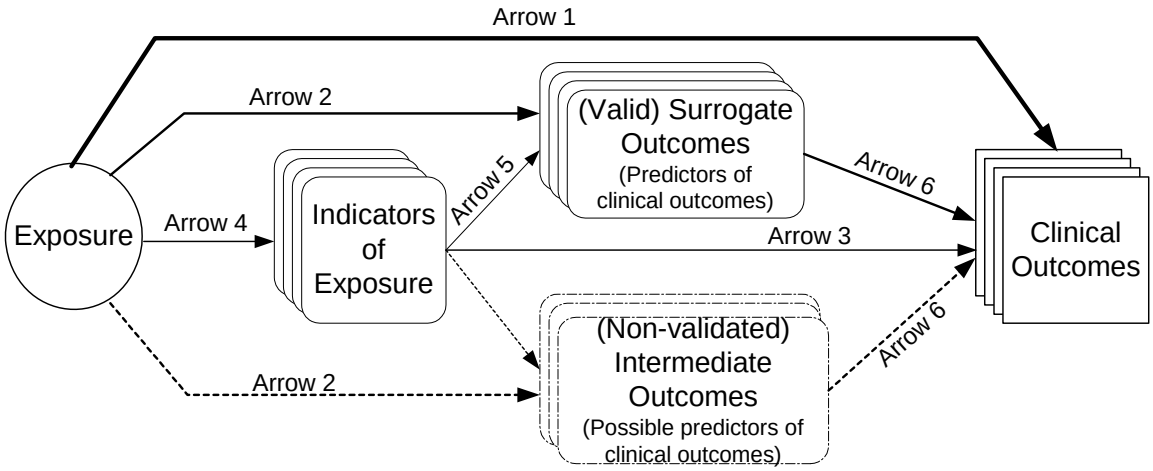
Key Questions Addressed in this Report

The aim of this report is to answer specific questions formulated to support the review and updating of DRI values by the DRI committee. The primary purpose of this report is to summarize all existing literature of vitamin D and calcium, and clinical outcomes in a way that will facilitate the deliberations of the IOM committee commissioned to review and potentially revise the DRI values for these nutrients. Specific clinical, surrogate and intermediate outcomes that are relating to vitamin D or calcium functions were selected by a technical expert panel. Detailed methods and analytic frameworks are described in Chapter 2. The intent of this report is not to make recommendations on specific outcomes nor specific values for DRI to be based upon, the intent of this report is to provide information for use during the deliberations of the IOM committee. The federal agencies of the US and Canadian governments involved in the DRI process formulated the key questions listed below based on the generic analytic framework as recently described (Figure 2).[3] The key questions are:

- What is the effect of exposures on functional or clinical outcomes? (Arrow 1)
- What is the effect of exposures on indicators of functional or clinical outcomes? (Arrow 2)
- What is the effect of indicators of exposure or body stores on functional or clinical outcomes? (Arrow 3)
- What is the effect of exposures on indicators of exposure? (Arrow 4)
- What is the effect of indicators of exposure or body stores and intermediate indicators of outcomes? (Arrow 5)
- What is the effect of intermediate indicators of outcomes and functional or clinical outcomes? (Arrow 6)

For each of these questions, the mandate was to also address factors that affect these relationships.

Figure 2. Generic analytic framework to assist formulation of key questions for the development of DRIs.



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.
Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 6: Association between surrogate outcomes (with good or possible evidence for linkage) and clinical outcomes.

The focus of this evidence report is on the relationship of vitamin D only, calcium only, and combinations of vitamin D and calcium to relevant health outcomes. Serum 25(OH)D concentration was used as an indicator of vitamin D status and calcium intake (dietary and supplement) as an indicator of calcium status. Evidence was sought for the life stages as defined in the DRI process. For the above questions, information relevant to benefit (efficacy) and safety (adverse effects) were considered. The questions were refined with input from a committee of vitamin D and calcium experts, discussed in the Methods chapter.

Chapter 2. Methods

Overview

This report is based on a systematic review of key questions on the relationships between vitamin D [either 25(OH)D concentrations or supplements] or dietary calcium intake, and health outcomes. The methodologies employed in this evidence report generally follow the methods outlined in the AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews (http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf). The initial questions identified by the federal sponsors of this report were refined with input from a Technical Expert Panel (TEP). This report does not make clinical or policy recommendations. The report is being provided to an IOM committee charged with updating vitamin D and calcium DRIs.

A description of roles and responsibilities of sponsoring federal agencies, AHRQ, the TEP and the EPC is included to clarify the relationships that support the process and ensure transparency and that the approach adhered to the highest standards of scientific integrity.

Because of the large number of abbreviations for unfamiliar terms are used, their explanations have been repeated whenever deemed necessary. A table of **Abbreviations** can be found after the references in page 316. We also provide a table with the latitudes of several major cities in Central and North America, right after the **Abbreviations** table, on page 320.

Sponsoring Federal agencies.

The sponsoring agencies were responsible for specifying the topic-specific task order requirements. They participated in a Kick-Off meeting with the EPC and the Task Order Officer (TOO) to facilitate a common understanding of the topic-specific work requirements, and responded to inquiries from the TOO if modifications to the work order were requested by the EPC. Any communication between the sponsoring agencies and the EPC occurred with oversight from the TOO.

Review by Federal sponsors was limited to comments on factual errors, requests for clarification, and consistency with the original contract task order. Comments on the scientific content of the report were not provided. In all cases, reviewer comments are advisory only and are not binding on the scientific authors of the final report.

AHRQ Task Order Officer (TOO).

The TOO was responsible for overseeing all aspects of this Task Order. The TOO served as the point person for all communication required between the sponsoring agencies, the EPC, and other AHRQ officials. The purpose of this communication was to facilitate a common understanding of the task order requirements among the sponsors, the TOO, and the EPC, resolve ambiguities and to allow the EPC to focus on the scientific issues and activities.

Technical Expert Panel (TEP).

The TEP is comprised of qualified experts including, but not limited to, individuals with knowledge of DRI decision making processes, vitamin D and calcium nutrition and biology across the life cycle, health outcomes of interest, and the methodology of conducting systematic reviews. The EPC worked closely with the TEP in the formative stages of the project on question

refinement and throughout the evidence review process to address questions that occurred. The EPC conducted the actual systematic review of the questions independent of the TEP and other stakeholders. It was specified, a priori, that a TEP member who served as a peer reviewer for the final report could not also serve as a member of the subsequent calcium and vitamin D DRI Committee.

Those serving on the TEP provided input on such factors as reviewing search terms to ensure they were adequately inclusive, assessing search strategies to ensure they comprehensively covered the questions of interest, and answering questions about technical details (e.g., nuances of laboratory methods of performing an assay). Members of the TEP did not participate in EPC research meetings or in reviewing and synthesizing evidence. Their function was limited to providing domain-specific knowledge and advising the proper context that is relevant to the process of evaluating DRI. They did not have any decision making role and did not participate in writing any part of the evidence report.

EPC methodologists.

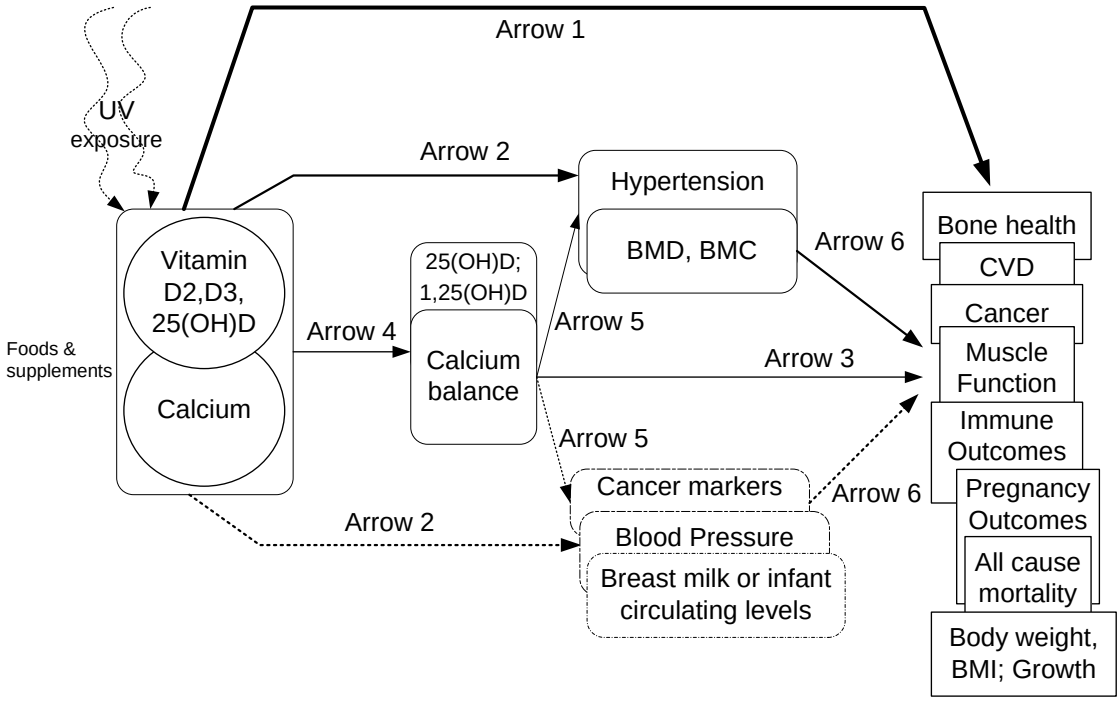
This evidence report was carried out under the AHRQ EPC program, which has a 12-year history of producing over 175 evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continually refine approaches to conducting evidence reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. The Tufts EPC has produced many evidence reports on nutrition topics[19-24] (http://www.ahrq.gov/clinic/epcix.htm). We have also conducted methodological research to identify the issues and challenges of including evidence-based methods as a component of the process used to develop nutrient reference values, such as the DRI, using vitamin A as an example.[3]

Development of the Analytic Framework and Refinement of Key Questions

The focus of this report is on the relationship of vitamin D only, calcium only, and combinations of vitamin D and calcium with specific health outcomes. Key questions and analytic frameworks were developed by defining each box in the generic analytic framework described in Chapter 1 with specific reference to vitamin D and calcium.

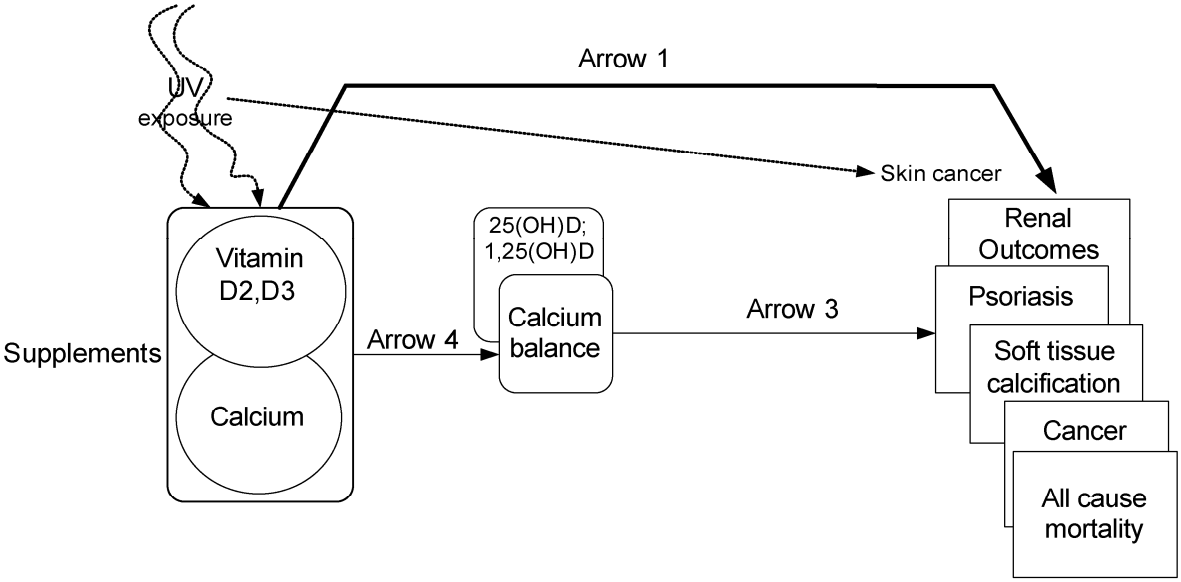
A one-day meeting of the federal sponsors, TEP and Tufts EPC staff was held in Boston on September 20, 2008. At this meeting, the analytic framework was discussed, the key questions refined, and study eligibility criteria established. Two analytic frameworks were developed: one for vitamin D and/or calcium Estimated Average Requirements (EARs) and one for Tolerable Upper Intake Levels (ULs) (Figures 3 & 4). We used the PI(E)CO method to establish study eligibility criteria. This method defines the Population, Intervention (or Exposure in the case of observational studies), Comparator, and Outcomes of interest. Details are described in the sections that follow.

Figure 3. Analytic framework for vitamin D and/or calcium EARs



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have good or possible evidence for linkage with clinical outcomes, respectively). (Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with dashed outline.)
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.
Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes.
Arrow 6: Association between surrogate or intermediate outcomes and clinical outcomes.

Figure 4. Analytic framework for vitamin D and/or calcium ULs



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.

Definitions

Vitamin D and Calcium Exposures

Vitamin D exposure included intake of vitamin D_2 or vitamin D_3 from foods and supplements, including human milk and commercial infant formulas. Because the primary source of vitamin D in the human body is produced in skin exposed to sunlight, background information on ultraviolet B (UVB) exposure was captured to the extent possible. However, we did not include studies that evaluated the effect of or association between exposure to sunlight (or UVB) and clinical outcomes or serum 25(OH)D concentrations. In other words, we did not investigate sunlight exposure as a proxy for or a source of vitamin D intake. Sunlight exposure was considered only as a potential confounder or effect modifier of associations between vitamin D or calcium and clinical outcomes.

Calcium exposure included intake of calcium from foods and supplements, including calcium-containing antacids, mineral-supplemented water, human milk and commercial infant formulas.

Combined vitamin D and calcium exposure included any relevant combinations of the above.

Clinical Outcomes

Clinical outcomes are measures of how a person (e.g., a study participant) feels, functions or survives, or a clinical measurement of the incidence or severity of a disease (e.g., diagnosis of disease or change from one disease state to another). Examples of clinical outcomes used in this report are incidence of cancer, vascular events, and preeclampsia. The clinical outcomes of interest in this report are described in the "Specific Outcomes of Interest" section.

Indicators of Exposure (Nutrient Intake)

Indicators of exposure are measures that correlate with dietary intake of a nutrient, such as nutrient biomarkers, nutritional status, or markers of nutritional status.

Indicators of vitamin D exposure (i.e., vitamin D intake and sun exposure) included serum 25(OH)D and $1,25(OH)_2D$ concentrations.

Indicators of dietary calcium intakes included calcium balance (i.e., calcium accretion, retention, and loss).

Surrogate Outcomes

Surrogate outcomes are biomarkers or physical measures that are generally accepted as substitutes for or predictors of specific clinical outcomes.[18] Changes induced by the exposure or intervention on a surrogate outcome marker are expected to reflect changes in a clinical outcome. Examples of surrogate outcomes used in this report are bone mineral density (as a surrogate marker of fracture risk) and breast mammographic density (as a surrogate marker of breast cancer risk). The surrogate outcomes of interest in this report are described in "Specific Outcomes of Interest" section.

Intermediate Outcomes

Intermediate outcomes are possible predictors of clinical outcomes that are not generally accepted to fulfill the criteria for a surrogate outcome. However, in the absence of data for surrogate outcomes, intermediate markers are often used. Examples of intermediate markers used in this report are prostate cancer antigen (as a marker of prostate cancer risk) and blood pressure (as a marker of stroke risk). All intermediate markers of interest in this report are described in "Specific Outcomes of Interest" section.

Life Stages

In consultation with the TEP, the 22 life stages defined by the FNB/IOM for the development of DRI were consolidated to 9 categories to facilitate the reporting of results. Within each life stages, men and women (or boys and girls) were considered separately when possible. There are also some inevitable overlaps between these categories. For example, most women in 51-70 years life stage are postmenopausal women. The 9 categories created for this report are:

- 0 – 6 months
- 7 months – 2 years
- 3 – 8 years
- 9 – 18 years
- 19 – 50 years
- 51 – 70 years
- ≥71 years
- Pregnant and lactating women
- Postmenopausal women

In summarizing studies for each given outcome, we used our best judgment to describe the study results for each applicable life stage.

Key Questions

In agreement with the TEP, the following key questions were addressed in this evidence report. It was decided that arrow 6 in the analytic framework (What is the relationships between intermediate or surrogate outcomes and clinical outcomes?) is outside the scope of the DRI literature review in this report. All outcomes of interest in this report are described in "Eligibility Criteria" section.

Key Question 1. What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification? (Arrow 1)

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

Key Question 3. What is the association between serum 25(OH)D concentrations or calcium balance and clinical outcomes? (Arrow 3)

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

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

Literature Search Strategy

We conducted a comprehensive literature search to address the key questions. For primary studies, the EPC used the Ovid search engine to conduct searches in the MEDLINE® and Cochrane Central database. A wide variety of search terms were used to capture the many potential sources of information related to the various outcomes (see Appendix A). Search terms that were used to identify outcomes of interest, for both EARs and ULs, can be categorized into the following groups: 1) body weight or body mass index; 2) growth (height and weight); 3) fracture or bone mineral density; 4) falls or muscle strength; 5) cardiovascular diseases; 6) hypertension or blood pressure; 7) cancer or neoplasms, including adenomas, colon polyps, and mammography; 8) autoimmune diseases (e.g., type 1 diabetes, psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, and Crohn's disease); 9) preeclampsia, eclampsia and pregnancy-related hypertension; 10) preterm or low birth weight; 11) breast milk or lactation; 12) death; 13) infectious diseases; 14) soft tissue calcification (for ULs only); and 15) kidney disease or hypercalcemia (for ULs only). The different outcomes were crossed with terms to identify vitamin D and calcium exposure: "vitamin D", "plasma vitamin D", "25-hydroxyvitamin D" and its abbreviations, "25-hydroxycholecalciferol", "25-hydroxyergocalciferol", "calcidiol", "calcifediol", "ergocalciferol", "cholecalciferol", "calciferol", "calcium", "calcium carbonate", "calcium citrate", "calcium phosphates" and

"calcium malate". Literature searches of the outcomes alone without references to vitamin D or calcium were not conducted.

The searches were limited to human studies, English language publications, and citations from 1969 to September 2008 for all but bone outcomes. For outcomes related to bone health (i.e., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC.[6] The Ottawa EPC report was updated from January 2006 to September 2008. The electronic search was supplemented by bibliographies of relevant review articles. Unpublished data, including abstracts and conference proceedings, were not included. An updated literature search was performed in April 2009 for all the topics to include relevant primary studies published since September 2008 for the final report.

For potentially relevant systematic reviews, we also searched MEDLINE®, the Cochrane Database of Systemic Reviews, and the Health Technology Assessments database up to December 2008. We searched for systematic reviews of the relationships between vitamin D or calcium and the prespecified outcomes. In this search, terms for identifying vitamin D or calcium exposures were crossed with terms for identifying systematic reviews, such as "systematic," "evidence," "evidence-based," "meta-analysis," or "pooled analysis"; specific terms for the outcomes were not included (Appendix B).

Study Selection

Abstract Screening

All abstracts identified through the literature search were screened. Eligible studies included all English language primary interventional or observational studies that reported any outcome of interest in human subjects in relation to vitamin D and/or calcium.

Full Text Article Eligibility Criteria

Articles that potentially met eligibility criteria at the abstract screening stage were retrieved and the full text articles were reviewed for eligibility. Rejected full text articles were examined only once, unless the articles were equivocal for inclusion or exclusion. In that event, the article in question was examined again by a different reviewer and a consensus was reached after discussion with the first reviewer. We recorded the reason for rejection of all full text articles.

Primary studies.

Because the outcomes of interest ranged from very broad topics with common occurrences (e.g., cardiovascular disease) to narrowly focused topics with relatively few occurrences (e.g., preeclampsia), the number and types of studies available for each outcome varied widely in the distribution of study designs and sample sizes. It was neither possible nor desirable to use a uniform, strict set of inclusion and exclusion criteria applicable to all outcomes. Therefore, additional eligibility criteria germane to the specific outcome were applied to all accepted full text articles. Details are described in the "Eligibility criteria" section.

General eligibility criteria for the full text articles were:

Population of interest:

- Primary population of interest is generally healthy people with no known disorders

- Studies that include a broad population that might have included some people with diseases. For example, some hypertensive and diabetic patients were included.
- People with prior cancers (or cancer survivors), prior fractures, and precancer conditions (e.g., colon polyps) were included
- Studies that enrolled more than 20 percent subjects with any diseases at baseline were excluded. An exception was made for older adults (mean age ≥65 years old) due to high prevalence of diseases in this population. For studies of older adults, only studies that exclusively enrolled subjects with particular disease (e.g., 100 percent type 2 diabetes) were excluded. In addition, for studies of blood pressure, studies of people exclusively with hypertension were included.
- For UL outcomes, we included any adverse effects of high intake in any population.

Intervention/exposure of interest.

- For observational studies:
    - Serum 25(OH)D or 1,25$(OH)_2$D concentration
    - Dietary intake level of vitamin D were not included due to inadequacy of nutrient composition tables for vitamin D.[25]
    - Dietary intake level of calcium from food and/or supplements
    - Calcium balance (i.e., calcium accretion, retention, and loss)
- For interventional studies:
    - Vitamin D supplements (but not analogues) with known doses
    - Calcium supplements with known doses
    - The only combination of dietary supplements of interest was the combination of vitamin D and calcium. Any other combinations of supplements and/or drug treatments were excluded unless the independent effects of vitamin D and/or calcium can be separated. Thus studies of multivitamins were excluded.
    - Trials in which participants in both study groups took the same calcium (or vitamin D) supplement were evaluated as vitamin D (or calcium) versus control trials. In other words, the intervention common to both study groups was ignored (though it was noted).
    - Food based interventions were included if the doses of vitamin D and/or calcium were quantified and there were differences in the doses between the comparison groups. For example, a trial of dairy supplementation (with 500 mg/d calcium) versus no supplementation was qualified to be included. However, a trial of calcium fortified orange juice (with 1200 mg/d calcium) versus milk (with 1200 mg/d calcium) was not qualified to be included because there are no differences in the calcium doses.
    - Non-oral routes of nutrient delivery were excluded

Specific outcomes of interest.

- Growth outcomes
    - In infants and premenarchal children: weight and height gain
- Cardiovascular disease clinical outcomes
    - Cardiac events or symptoms (e.g., myocardial infarction, angina)
    - Cerebrovascular events (stroke, transient ischemic attacks)
    - Peripheral vascular events or symptoms (diagnosis, claudication)

    - Cardiovascular death
    - Study-specific combinations of cardiovascular events
- CVD intermediate outcomes
    - Diagnosis of hypertension
    - Blood pressure
- Weight outcomes
    - In adults only: incident overweight or obesity, body mass index, or weight (kg)
- Cancer (incident or mortality)
    - Cancer from all cause (or total cancer)
    - Prostate
    - Colorectal cancer
    - Breast cancer
    - Pancreatic cancer
    - Cancer-specific mortality
- Cancer intermediate outcomes
    - Colorectal adenoma
    - Aberrant cryptic
    - Breast mammographic density (quantitative whole breast density)
- Immune function clinical outcomes
    - Infectious diseases
    - Autoimmune diseases
    - Infectious disease-specific mortality
- Pregnancy-related outcomes
    - Preeclampsia
    - High blood pressure with or without proteinuria
    - Preterm birth or low birth weight
    - Infant mortality
- Mortality, all cause
- Bone health clinical outcomes
    - Rickets
    - Fracture
    - Fall or muscle strength
- Bone health intermediate outcomes
    - Bone mineral density or bone mineral content
- Dose-response relationship between intake levels and indicators of exposure (arrow 4 of Figures 2 and 3)
    - Serum 25(OH)D concentration
    - Breast milk or circulating concentrations of 25(OH)D in infants
- Outcomes of tolerable upper intake levels (ULs)
    - All-cause mortality
    - Cancer and cancer-specific mortality
    - Renal outcomes
    - Soft tissue calcification
    - Adverse events from vitamin D and/or calcium supplements

Study design.

- Randomized controlled trials (RCTs)
- Nonrandomized, prospective comparative studies of interventions
- Prospective, longitudinal, observational studies (where the measure of exposure occurred before the outcome)
- Prospective nested case-control studies (case-control study nested in a cohort so the measure of exposure occurred before the outcome)
- We excluded cross-sectional studies and traditional, retrospective case-control studies (where the measure of exposure occurred after or concurrent with the outcome)

Systematic reviews.

We included relevant systematic reviews that addressed the key questions. Systematic review is defined as a study that has at a minimum the following three components: a statement of the research questions (aims or objectives); a description of the literature search; and a listing of the study eligibility criteria. We did not attempt to contact authors for clarifications of outstanding questions. In addition, the following types of reviews were excluded: reviews of foods or diets that did not quantify vitamin D or calcium intake; reviews that included non-oral routes of nutrient delivery; reviews that did not evaluate the association between vitamin D or calcium intake to health outcomes; reviews of nonhuman data; and pooled analyses of primary databases (i.e., secondary database analyses of multiple cohorts) that did not include a systematic review (except possibly as a replacement for data from the original cohorts).

To determine the relevance of a systematic review to this report, the following inclusion criteria were applied:

- Address key question(s) of interest (i.e., similar PI(E)CO criteria used):
    a. Systematic review must include only healthy population at baseline or have separate analyses for population with diseases and without diseases.
    b. Systematic reviews of interventional studies had to include only vitamin D or calcium interventions. Cointerventions with other nutrients had to be disallowed or separate analyses were needed for studies of vitamin D or calcium interventions alone.
    c. Systematic review of observational studies had to report the baseline concentrations of serum 25(OH)D and the assay methods used or the dietary assessment methods used to measure dietary calcium intake (e.g. food frequency questionnaire, 24 hour recall).
    d. Exposure levels (e.g., level of 25(OH)D or calcium intake) or doses of interventions had to be reported
    e. Outcome definitions had to be reported
    f. Designs of primary studies had to be reported. If cross-sectional or case-control studies were included, the systematic review must provide sufficient information or separate analyses to separate them from RCTs or cohort studies.
- We include only the most recent update if there were multiple systematic reviews from the same group of investigators using the same review process.
- Where there were several systematic reviews on the same topic with similar conclusions and the same set of primary studies, we selected the systematic review with either the latest cutoff date for the end of the literature search or the most included primary studies.

Other Specific Eligibility Criteria

- Growth outcomes (weight and height gain)
    - Only infants (<1 year old) and children (age <18 years old) were included
    - For infants, we include all eligible study designs. The vitamin D and/or calcium intervention or exposure can be administered to the mothers or to the infants in the study.
    - For infants, premenarchal girls, and boys of similar age, only RCTs that reported weight as a primary or secondary outcome were included. RCTs of weight loss were excluded.
- Cardiovascular disease clinical outcomes
    - Only adults (aged ≥18 years old) were included.
- Blood pressure and body weight
    - Only adults (aged ≥18 years old) were included.
    - Only RCTs of calcium or vitamin D interventions were included. We did not include observational studies of associations between calcium or vitamin D intake or serum vitamin D concentrations and blood pressure or weight measurements (as continuous outcomes). This decision was made in agreement with the TEP in part because it was agreed that any conclusions based on observational studies (e.g., associations between baseline calcium intake and change in systolic blood pressure) would be weak and difficult to interpret.
- Bone health clinical outcomes
    - The Ottawa EPC report[6] was updated with literature published between January 2006 and September 2008. Only RCTs qualified for inclusion.
    - Studies of calcium and bone health clinical outcomes were excluded.
- Bone health intermediate outcomes
    - The Ottawa EPC report[6] was updated with literature published between January 2006 and September 2008. For adults, we included only BMD indices. For children, we included only BMC indices. Only RCTs with duration of more than 1 year were qualified for inclusion.
    - Studies of calcium and bone health clinical outcomes were excluded.
- Dose-response relationship between intake levels and indicators of exposure (arrow 4 of Figures 2 and 3)
    - Studies for this question were identified in our literature search that crossed vitamin D terms with various outcomes terms. Some studies that addressed this question but do not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all full text articles mentioning vitamin D supplements (in excess of 10,000) to look for data on serum 25(OH)D concentration.

- Only RCTs were included for this question. However, RCTs of different regimens but with the same dose of vitamin D supplementation were excluded (e.g., comparison of daily, weekly versus monthly dose).

Data Extraction

For outcomes that had not been subjected to a prior systematic review, we extracted and summarized the relevant data from the primary studies. Where previous systematic reviews were available, we summarized their results into our report. In addition, we updated the previous systematic reviews (with our eligibility criteria) and extracted and summarized the additional primary studies.

Data extraction forms (evidence tables) were developed separately for extraction of systematic reviews and primary studies. For primary studies, the items extracted were: study characteristics, baseline population characteristics, background diet data, dietary assessment methods for calcium intake, 25(OH)D assay methods, interventions (for interventional studies only), confounders and effect modifiers that were adjusted for in statistical analysis, results, and quality assessments. Whenever the type of vitamin D supplement (D_2 or D_3) was clearly reported, we extracted and reported this information. Otherwise, we used the general term "vitamin D". Evidence tables for all eligible studies are available in Appendix C. For systematic reviews, items extracted were: design, population, intervention (exposure) and comparator, results, and AMSTAR[26] checklist criteria (a measurement tool created to assess the methodological quality of systematic reviews). A table with a list of all systematic reviews with the evaluation of their relevance to this report, and evidence tables of the qualified systematic reviews are available in Appendix D.

Data Analysis

We explored the dose-response relationship between the level of intake of vitamin D (with or without calcium) and serum 25(OH)D concentrations graphically, using a scatter ("bubble") plot. We plotted the observed net changes in 25(OH)D concentration, against the doses of vitamin D supplementation. In these plots studies were represented by empty circles (bubbles) with area proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Studies were included only if they reported sufficient data to estimate both mean net change and SE of the net change. We required data on both the mean net change in outcome level and the SE of the change. However, many studies provided only the SEs for the baseline and final outcome levels. In order to include these studies in the analyses we had to make several assumptions to estimate the SE of the change. To do this we used the equation:

$$SE_{12} = \sqrt{(SE_1^2 + SE_2^2 - 2\rho SE_1 SE_2)}$$

where SE_1, SE_2, and SE_{12} are the SEs for baseline, final and change, respectively, and ρ is the correlation between the baseline and final measurements.[27] We arbitrarily chose the correlation, ρ, to be 0.50, the midpoint value. In our experience, using different values for ρ generally does not greatly affect the meta-analysis results of quantitative analyses or conclusions.

For each RCT, the SE of the net change was then calculated using the standard calculation for determining the SE of 2 independent cohorts. Namely, in the above equation where the correlation factor ρ becomes 0, and thus the final term drops out. Where studies reported either within-cohort SEs or net change SEs, these numbers were used. Some RCTs may have more than

two arms (e.g., two different doses of vitamin D supplement compared to the placebo), and in this case, the same control arm was used to calculate the net change and the SE of the net change as for two independent comparisons.

Meta-analysis

Overall, we did not perform new meta-analyses in this report because of large degree of clinical and methodological heterogeneity across studies. However, we reanalyzed an existing meta-analysis using available data in the all-cause mortality section. We performed random effects model meta-analyses of risk ratios using the DerSimonian and Laird model.[28] The random effects model assigns a weight to each study that is based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it results in broader confidence intervals when between-study heterogeneity is present. We tested for heterogeneity using Cochran's Q (considered significant for $P < 0.10$) and quantified its extent with I^2 [29,30]. I^2 ranges between 0 and 100 percent and quantifies the proportion of between-study variability that is attributed to heterogeneity rather than chance.

Intercooled Stata SE version 9.2 and Meta-Analyst version 3.2 (developed by Tufts EPC) were used for analyses. All P values are two tailed and considered significant when less than 0.05, unless otherwise indicated.

Grading of Studies Analyzed in This Evidence Report

Studies included as part of accepted in this report have been designed, conducted, analyzed, and reported with various degrees of methodological rigor and completeness. Deficiencies in any of these items may lead to biased reporting or interpretation of the results. While it is desirable to have a simple evidence grading system using a single quantity, the quality of evidence is multidimensional. A single metric cannot adequately capture information needed to interpret a study. Not withstanding these limitations, providing an indication of study quality adds an important dimension to the summary of published data.

Critical Appraisal and Grading of Primary Studies

Critical appraisal of the evidence is an important aspect of conducting a systematic review. For the assessment of interventional studies, the criteria were based on the CONSORT[31] statement for reporting RCTs (a checklist with specifications for reporting important aspects of a trial). We primarily considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of well-described valid primary outcomes, and the dropout rate.

For interventional studies with nonrandomized design, we used the report of eligibility criteria and assessed the adequacy of controlling for differences between compared groups in terms of baseline characteristics and prognostic factors. We also considered the reporting of intention-to-treat analyses and crossovers when so designed, as well as important differential loss to followup between the compared groups or overall high loss to followup. The validity and the adequate description of outcomes and results were also assessed.

For the assessment of prospective cohorts and nested case-control studies (cross-sectional and retrospective case-control studies were excluded from this review), we developed a rating checklist specifically designed for nutritional epidemiology study based on some of the reporting items for cohort study in STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist[32] and the nutrition-specific items in our previous publication.[33] Items assessed include: eligibility criteria and sampling of study population, blinding of exposure and outcome assessors, dietary assessment methodology (when applicable), assay methodology of biomarkers of intake (when applicable), clear reporting of comparisons in the study, statistical analyses, adequacy of controlling for baseline characteristics and prognostic factors (including confounders), clear reporting of outcome definitions, and prospective study design with preplanned hypotheses.

The quality assessment checklists for intervention or observational studies can be found in Appendix E. Additional considerations that were not included in the checklists are described later in this section.

In this report we adapted a three-category grading system of the AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. This system defines a generic grading system that is applicable to each type of study design including interventional and observational studies:

A

Studies have the least bias and results are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a formal study design; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias. Studies must provide valid estimation of nutrient exposure, from dietary assessments and/or biomarkers with reasonable ranges of measurement errors, and justifications for approaches to control for confounding in their design and analyses.

B

Studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A", they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C

Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or discrepancies in reporting.

If the initial assigned grade was equivocal, then the study received a second round of review by an independent reviewer, and the final grade was reached via consensus. Lastly, it should be noted that the quality grading system evaluates and grades the studies within their own design strata (i.e., RCTs, cohorts, nested case-control). It does not attempt to assess the comparative validity of studies across different design strata. Thus, it is important to be cognizant of the study design when interpreting the methodological quality grade of a study.

Additional Considerations of Methodological Quality of Primary Studies for the Purpose of DRI Decision Making

Randomized controlled trials of all outcomes.

The Tufts EPC debated about the quality assessment of RCTs. A consensus was reached to include additional considerations for RCTs to receive grade A. The general quality assessment of interventional studies as described earlier has been widely adopted for the purpose of grading high quality effectiveness trials (in contrast with a more standardized efficacy trial) which are most relevant to the actual use of supplements. Thus the crossover of interventions (i.e., contamination between supplementation and placebo groups) affects the applicability more than the methodological quality. However, it was the consensus among the Tufts EPC methodologists that the RCTs with contamination between supplementation and placebo groups cannot receive grade A because this issue affects the actual differences in the doses given to the subjects. Therefore it is particularly important when the trial results are used to guide decisions about DRI, as opposed to decisions about whether to actively recommend supplementation for an individual.

Observational studies of cancer outcomes.

When cancer cases were identified based on cancer registries or questionnaire-based data, we perused whether the investigators verify the diagnoses independently (e.g., by medical records or pathological reports). An observational study of cancer outcomes cannot receive grade A if the cancer diagnoses were not verify independently. We also examined if the study adequately control for other risk factors for specific cancer. We used the suggested risk factors by National Cancer Institute (www.cancer.org). An observational study of cancer outcomes cannot receive grade A if important risk factors for the specific cancer were not fully controlled for in their analyses.

Critical Appraisal of Systematic Reviews

We also critically appraised systematic reviews utilized in this report. However, a summary quality grade for systematic review is difficult to interpret. While it may be straightforward to assign a high quality grade to a rigorously carried out systematic review of high quality primary studies, a rigorously conducted systematic review finding only poor quality primary studies to summarize has uncertain value. Similarly, a poorly conducted systematic review of high quality studies may also result in be misleading conclusions. Therefore, to appreciate its validity, the various dimensions and nuances of the systematic review must be understood.

To help readers appreciate the methodological quality of a systematic review, we applied the AMSTAR checklist,[26] a tool that was created for this purpose. This tool does not assign a composite grade. Instead, the items evaluated are made explicit for the reader. Another challenge in evaluating systematic reviews is that none of the existing systematic reviews were specifically conducted to be used for DRI development; therefore their "quality", for the purpose of DRI development, is impossible to reliably define.

In addition to using AMSTAR, we made comments on special considerations, issues or limitations concerning design, conduct and analyses of the systematic review, and interpretability of the results for the purpose of DRI development.

Reporting of the Evidence

Evidence tables.

Evidence tables offer a detailed description of the primary studies we identified that address each of the key questions. These tables provide detailed information about the study design, patient characteristics, background diet, inclusion and exclusion criteria, interventions (or exposures), comparators used, and outcomes assessed in the study. A study, regardless of how many interventions (or exposures) or outcomes were reported, appears once in the evidence tables. Evidence tables are ordered alphabetically by the first author's last name to allow for easy searching within the tables. Evidence tables are available electronically in Appendix C.

Summary tables.

Summary tables were created to assist (qualitative) synthesis of primary studies of the same outcomes and life stage. If feasible, data were also grouped by sex. Typically, in each outcome section, we presented one summary table for the study characteristics of all included studies, followed by another summary table for study findings.

We created different summary tables for different exposures (i.e., vitamin D or calcium) and for different study designs (i.e., interventional or observational studies). Key study characteristics, such as population characteristics (i.e., health status, age and sex), vitamin D assay method and season in which blood was drawn, dietary assessment methods and whether the instrument was internally validated, patient or participant adherence, and study comparisons, were presented in the summary table for study characteristics. We reported daily vitamin D doses (IU/d) and/or elemental calcium doses (mg/d) in all summary tables.

For observational studies, we also list the confounders adjusted in either design (e.g., matching factors) or analyses. If any confounders or effect modifiers in each prespecified category (i.e., nutrients, demographics, anthropometry, medical conditions, ultraviolet exposure, and life styles) were controlled for, we marked "X" in the category. Otherwise, the category was left blank.

Graphical presentation of dose-response relationship.

We present graphically the results of studies associating outcomes with categorical exposures (e.g., percentiles or other arbitrary categories of 25(OH)D concentration or of total calcium intake). The graphs complement the information mentioned in the tables and allow the reader to appreciate the direction of the estimated effects, even when the choice of the reference category is inconsistent across studies. The graphs do not readily convey the slope (strength) of the dose-response relationship between exposure and outcome, because the exposure categories are simply ranked and their spacing does not necessarily correspond to the actual values that they represent within study or across studies.

Grand summary tables (evidence map).

In the beginning of the Results section, we created a grand overview table. The table details how many studies reported an outcome of interest (either as a primary or non-primary outcome) and also listed the total number of unique studies (including systematic reviews) as each study may have provided data on more than one outcome. The number of primary studies included in each existing systematic review is also reported.

Units of measurement.

In this report, we converted serum 25(OH)D concentrations as reported by various studies as different units (i.e., ng/mL, μg/dL, μg/L and ng/dL) to nmol/L. The conversion formula is 1 ng/mL = 2.5 nmol/L. To limit the variation in the reporting of vitamin D unit (e.g., nmol, IU, μg and mg), IU was chosen as the standard unit and all other units were converted using a standard formula. The conversion formula for micrograms is 1 μg = 40 IU.

Assay method.

For 25(OH)D measurements, we present information on the assay used in our evidence tables, and summary tables describing individual studies. When reported, we also recorded details on the methodology or kit used (e.g., RIA–radioimmunoassay, RIA "DiaSorin") used. Often, additional information was lacking. We did not perform any subgroup analyses based on the type of 25(OH)D assay used.

Sunlight exposure.

We report information on country where the study took place and its latitude (when this was meaningful), and when available, the season when serum 25(OH)D concentrations were measured. A substantial amount of vitamin D is formed in the skin in humans. The amount of vitamin D synthesized in the skin depends on a person's exposure to UV irradiation. Therefore, information on country's latitude (and season of serum 25(OH)D measurements) informs on whether different populations are likely to have similar or different amount of endogenous vitamin D production. Latitudes were extracted directly from the published reports, or extrapolated from the city or country where the study took place (by searching Google for "<county/city> latitude"). For national or international studies that spanned a wide range of latitudes (e.g., NHANES), the latitude information was summarized simply as "various." To facilitate the reader, we also provide a Table with the latitudes of major cities in Central and North America (this table is found right after the **Abbreviations** table on page 316.

Primary and secondary outcomes.

For intervention studies, we distinguished primary from secondary (or nonspecified) outcomes. Outcomes were considered primary only when they were clearly reported as such or when the outcome was used in an ad hoc sample size calculation. For observational studies we did not separate primary from secondary outcomes. For example, many observational studies are analyses of the same well known cohorts for several different outcomes. Each of these studies may have a different "primary" outcome.

Study quality.

We summarize methodological and reporting quality of individual studies and meta-analyses. More details on the reporting characteristics of individual studies and systematic reviews are found in the evidence tables (Appendix C).

Organization of the results section.

The Results section is organized in the following way:

- Nutrient (vitamin D | calcium | combined calcium and vitamin D)
    - Outcome (e.g., growth, cardiovascular diseases)
        - Synopsis
        - Detailed presentation (depending on availability of data)
            - Findings per calcium intake level / vitamin D concentration
            - Findings per age and sex
        - Findings by life stage

Chapter 3. Results

Literature Search Results

The original MEDLINE® and Cochrane Central database search for primary studies yielded 15,621 citations of EAR outcomes and 194 citations of UL outcomes. The update search for primary studies published between September, 2008 and April, 2009 yielded 918 citations We identified 654 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these, 478 did not meet eligibility criteria (Appendix E); thus, a total of 165 primary study articles met the inclusion criteria and were included in this report (Figure 5). Of the 165 primary study articles, 60 were randomized controlled trials (RCTs), 3 were nonrandomized comparative studies, and 102 were observational studies (either cohort or nested case-control studies). The publication dates of the 165 primary study articles ranged from 1980 to 2009.

The MEDLINE®, Cochrane Database of Systemic Reviews, and the Health Technology Assessments database search for systematic reviews yielded 1746 citations. We identified 68 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these, 46 did not meet eligibility criteria. After examining the 22 qualifying systematic reviews, 11 were excluded for various reasons (Appendix D; Figure 5).

The grand overview tables (Tables 1, 2, and 3) detailed how many studies reported an outcome (either as a primary or secondary outcome) that is of interest and also listed the total number of unique studies (including those from systematic reviews) as each study may have provided data for more than one outcome.

Figure 5. Literature flow in this report

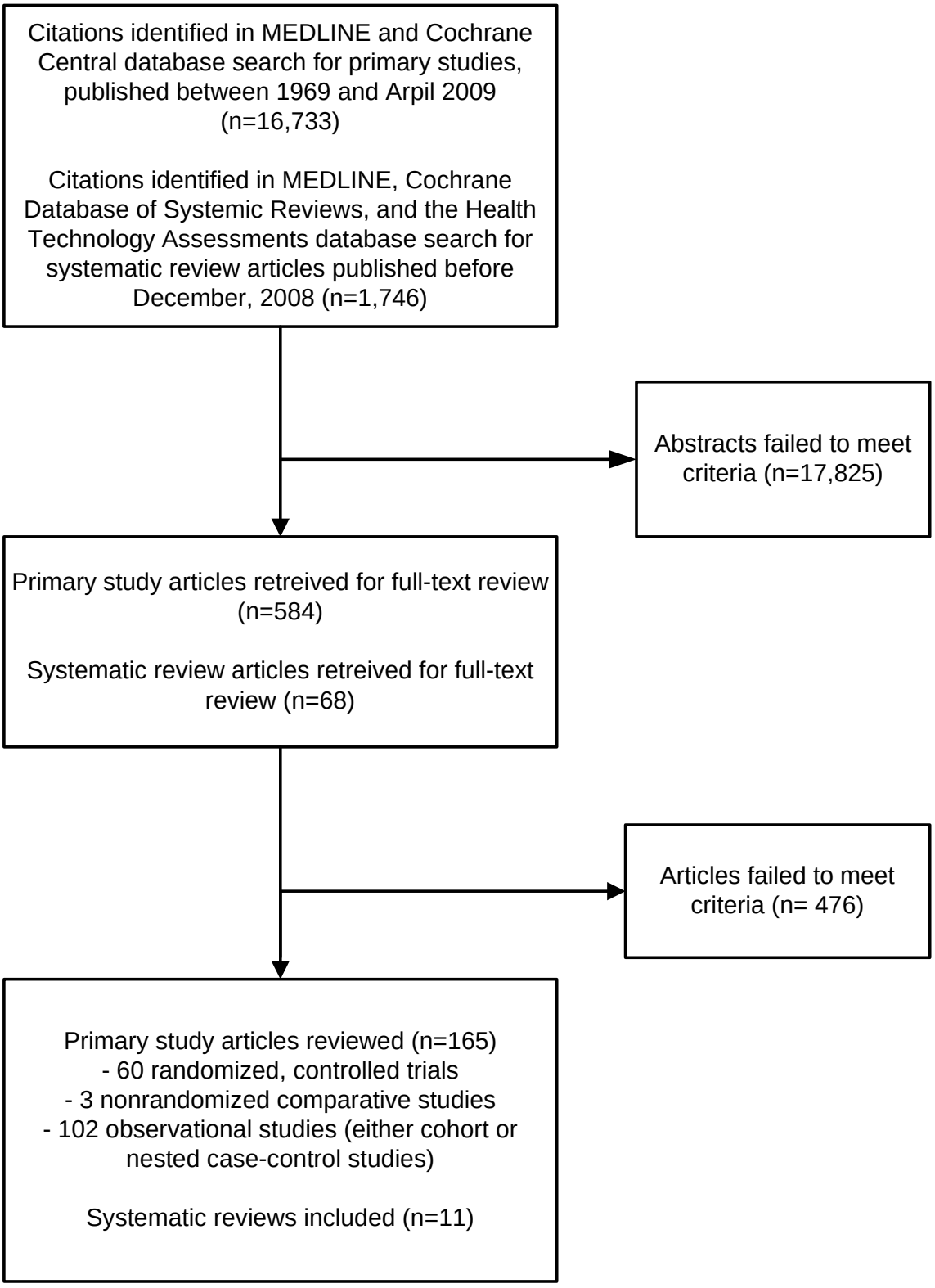


Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages

	Growth	CVD clinical	Body weight (adults)	Total cancer	Prostate cancer	Colorectal cancer	Colorectal adenoma	Breast cancer	Breast mammographic density	Pancreatic cancer	Immune function clinical outcomes	Preeclampsia & pregnancy outcomes	All-cause mortality	Bone health clinical outcomes	Bone mineral density or content	Hypertension	Blood pressure
0 – 6 mo	8																
7 mo – 2 y	1										1[B]						
3 - 8 y																	
9 – 18 y	2														2		
19 – 50 y		1	1	1	2	1		1			1				1	1	1
51 – 70 y		3	2	1	10	6	1	2		2	1		8		1	1	1
≥71 y		2		1		1					1		8	3		1	2
Pregnant & lactating women	7										1	1					
Postmenopause		1	1	1		1					1[B]					1	2
Total unique studies per outcome	**9**	**5**	**3**	**3**	**12**	**9**	**1**	**3**	**0**	**2**	**2**	**1**	**8**	**3**	**3**	**2[C]**	**3**
[Total number of RCTs per outcome]	**[6]**	**[1]**	**[3[A]]**	**[2]**	**[0]**	**[1]**	**[0]**	**[0]**		**[0]**	**[0]**	**[0]**	**[8]**	**[3]**	**[3[A]]**	**[0]**	**[3[A]]**
Systematic reviews (unique studies) per outcome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (4)**	**1 (73)**		**0**	**0**

Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.

[A] Only RCTs were eligible for this outcome
[B] Relationship between maternal 25(OH)D concentration and atopic eczema in infants
[C] 1 study was a combined analysis of Nurses Health Study and Health Professionals Follow-up Study

Table 2. Number of primary studies on calcium intake and specific health outcomes that could be applicable to certain life stages

	Growth	CVD clinical	Body weight (adults)	Total cancer	Prostate cancer	Colorectal cancer	Colorectal adenoma	Breast cancer	Breast mammographic density	Pancreatic cancer	Immune function clinical outcomes	Preeclampsia & pregnancy outcomes	All-cause mortality	Bone health clinical outcomes	Bone mineral density or content	Hypertension	Blood pressure
0 – 6 mo	1																
7 mo – 2 y																	
3 - 8 y	1					1[B]											
9 – 18 y	3																
19 – 50 y		2	3	1		3		1	1	1			1			5	3
51 – 70 y		9	5	1	12	17	6	5		2			1			4	2
≥71 y		1	1	1		1[B]				1							2
Pregnant & lactating women	1											14					
Postmenopause		1	4	1				4								1	2
Total unique studies per outcome	**3**	**11**	**8**	**3**	**12**	**21**	**6**	**6**	**1**	**2[C]**	**0**	**14**	**1**			**5[D]**	**5**
[Total number of RCTs per outcome]	**[1]**	**[0]**	**[8[A]]**	**[2]**	**[0]**	**[0]**	**[1]**	**[0]**	**[0]**	**[0]**						**[0]**	**[5[A]]**
Systematic reviews (unique studies) per outcome	**1 (17)**	**0**	**3 (41)**	**0**	**0**	**1 (2)**	**1 (2)**	**0**	**0**	**0**	**0**	**1 (12)**	**0**			**0**	**6 (64)**

Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.

[A] Only RCTs were eligible for this outcome
[B] Association between total calcium intake in childhood and colorectal cancer after 65 years of followup
[C] 1 study was a combined analysis of Nurses Health Study and Health Professionals Follow-up Study
[D] 6 analyses, including 2 separate analyses of NHANES I

Table 3. Number of primary studies on combined vitamin D and calcium intake and specific health outcomes that are relevant to certain life stages

	Growth	CVD clinical	Body weight (adults)	Total cancer	Prostate cancer	Colorectal cancer	Colorectal adenoma	Breast cancer	Breast mammographic density	Pancreatic cancer	Immune function clinical outcomes	Preeclampsia & pregnancy outcomes	All-cause mortality	Bone health clinical outcomes	Bone mineral density or content	Hypertension	Blood pressure
0 – 6 mo	1																
7 mo – 2 y																	
3 - 8 y																	
9 – 18 y															1		
19 – 50 y			1											1			1
51 – 70 y		1	1				1						3			1	1
≥71 y			1										8				
Pregnant & lactating women	1											1					
Postmenopause		1	1	2		1	1	1					8	1	3	1	1
Total unique studies per outcome	**1**	**1[B]**	**2[B]**	**2[B]**	**0**	**1[B]**	**2[B]**	**1[B]**	**0**	**0**	**0**	**1**	**11[BC]**	**2[B]**	**4**	**1[B]**	**2[B]**
[Total number of RCTs per outcome]		**[1]**	**[2[A]]**	**[2]**		**[1]**	**[1]**	**[1]**					**[11]**	**[2]**	**[4[A]]**	**[1]**	**[2[A]]**
Systematic reviews (unique studies) per outcome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (10[B])**		**1 (119[B])**	**0**	**0**

Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.

[A] Only RCTs were eligible for this outcome
[B] Including the Women's Health Initiative (WHI) trial
[C] A de novo reanalysis of the 10 RCTs in a previous systematic review and one newly added trial

Vitamin D and Health Outcomes

Vitamin D and Growth

We reviewed primary studies that evaluated relationships between vitamin D and growth parameters in infants and children.

Synopsis.

Seven intervention studies and two observational studies evaluated intake of or exposure to vitamin D and growth parameters in infants and children. Two intervention studies from the same center found a significant association of maternal vitamin D intakes with infant birth weights. Study methodologies were incompletely reported in these two studies. The rest of the studies did not find a significant association between either maternal or offspring vitamin D intake and offspring's weight or height. No overall conclusions could be drawn as the studies reviewed had diverse populations and methodological approaches.

Detailed presentation (Tables 4, 5, 6 & 7).

Six RCTs[34-40] and one nonrandomized comparative study[41] in eight publications reported on the effect of vitamin D supplementation on growth parameters in infants and children. Two cohort studies reported on the association between maternal serum 25(OH)D concentration and her offspring's growth parameters.[42,43] The number of subjects in the RCTs ranged from 19 to 200. The two cohort studies had 374 and 466 subjects, respectively. The latitudes of the studies ranged from 38º to 51º. Four studies administered vitamin D exclusively to expectant mothers during the third trimester of pregnancy. One study administered vitamin D to both the lactating mothers and her offspring. Two studies administered vitamin D only to the infants or children. Followup ranged from delivery until 9 years. Methodological quality of two studies were rated B and seven studies were rated C. The studies were limited by such factors as incomplete reporting and small sample sizes.

Infant 0 - 6 months; 7 months - 2 years; pregnant or lactating women.

One RCT from UK administered vitamin D 1000 IU/d or placebo to 126 expectant mothers (first generation Asian immigrants) during the third trimester and found no significant difference between the infants' birth weights or birth lengths and those of the control population.[34,38] There were twice as many low birth weight infants (<2500 g) in the control group compared to the supplemented group (21.7 percent vs. 11.9 percent); however, this difference was not significant. A study from US supplemented 10 lactating mothers with vitamin D 400 IU/d and their infants with 300 IU/d for 6 months. Compared to the group where nine mothers received 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age.[39] A study from China randomly assigned 255 newborn infants to 100, 200, or 400 IU/d of vitamin D for 6 months and reported no significant difference in weight or length among the three groups at 6 months of age.[36] One study from India randomly selected 100 expectant mothers to receive a total of 1.2 million IU of vitamin D (600,000 IU of vitamin D_2 in 7^{th} and 8^{th} month) during the third trimester. The newborns' birth weight was significantly increased compared to those from 100 unsupplemented expectant mothers (difference 190 g).[37] Important elements of the study methodology like randomization technique and any blinding of outcome assessors were not reported. An earlier nonrandomized comparison from the same study center involving smaller samples reported similar findings.[41] The estimated baseline mean

dietary vitamin D intake in the expectant mothers from these two studies was less than 30 to 35 IU/d (the validity of these measures is unclear). An RCT from France supplemented 48 expectant mothers with either vitamin D 1000 IU/d in the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods.[40] A cohort study from Australia analyzed the maternal serum 25(OH)D concentration in 374 women at 28-32 week gestation (geometric mean in winter 48 nmol/L; summer 69 nmol/L) and found no association with infant birth weight or length.[43] One cohort study from UK analyzed the serum 25(OH)D concentration in 466 white women in late pregnancy (~33 wk) and found the concentrations (from <30 to >75 nmol/L) were not related to their offspring's weight or height at birth, 9 months, and 9 years.[42]

9 - 18 years.

One RCT of vitamin D_3 (placebo, 200, or 2000 IU/d for 1 year) on girls in Lebanon aged 10-17 years found no significant difference at 1 year followup in weight or height among the 34 girls who were premenarchal at time of enrollment.[35]

Findings by life stage.

- **0 – 6 mo** One RCT found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length. Another RCT found that supplementing expectant mothers with a total of 1.2 million IU of vitamin D during the 3rd trimester effected a significant increase in birth weight (+190 g). Background diet is low in vitamin D in this study. A study compared supplementing lactating mothers with vitamin D 400 IU/d and their infants 300 IU/d for 6 months with mothers supplemented with 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age. Another study compared supplementing newborn infants with 100, 200, or 400 IU/d of vitamin D for 6 months and reported no significant difference in weight or length at 6 months of age. An RCT supplemented expectant mothers with either vitamin D 1000 IU/d during the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods. A cohort study analyzed the maternal serum 25(OH)D concentration at 28-32 week gestation (geometric mean in winter 48 nmol/L; summer 69 nmol/L) and found no association with infant birth weight or length. Another cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.
- **7 mo – 2 y** A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.
- **3 – 8 y** No study covered this life stage.
- **9 – 18 y** A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years. One RCT of vitamin D_3 (placebo, 200, or 2000 IU/d for 1 year) on girls 10-17 years old found no significant difference at 1 year followup in weight or height among the girls who were premenarchal at time of enrollment.
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed

- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** One RCT found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length. Another RCT found that supplementing expectant mothers with a total of 1.2 million IU of vitamin D during the 3rd trimester effected a significant increase in birth weight (+190 g). Background diet is low in vitamin D in this study. A study compared supplementing lactating mothers with vitamin D 400 IU/d and their infants 300 IU/d for 6 months with mothers supplemented with 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age. An RCT supplemented expectant mothers with either vitamin D 1000 IU/d during the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods.

Table 4. Vitamin D on growth outcome: Characteristics of interventional studies

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
RCTs						
Maxwell 1981[38] Brooke 1980[34] UK (51ºN) [6793058] [6989438]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy nd 0	25(OH)D at 28-32 wk: 20.1 nmol/L	Vit D 1000 IU/d 3rd trimester only	nd	First generation Asian immigrants only
Feliciano 1994[36] China (22ºN to 47ºN) [8078115]	• Health status • Mean age (range/SD), y • Male (%)	healthy term newborn nd	86% infant breastfed until 5-6 mo	Vit D 100 IU/d vs. 200 IU/d vs. 400 IU/d	nd	
El-Hajj 2006[35] Lebanon (33ºN) [16278262]	• Health status • Mean age (range/SD), y • Male (%)	healthy 13.2 (10-17) 0	25(OH)D 35 nmol/L; dietary Ca 677 mg/d	Vit D_3 200 IU/d vs. 2000 IU/d vs. placebo x 1 y	98% in placebo; 98% in low dose; 97% in high dose	7.4 h sun exposure/wk
Wagner 2006[39] Charleston, US (32ºN) [17661565]	• Health status • Mean age (range/SD), y • Male (%)	Fully lactating; <1 mo postpartum 29 0	Lactating mother's dietary Vit D 273 IU/d; dietary calcium intake: 1125 mg/d;	Mother Vit D_3 400 IU/d + infant 300 IU/d vs. mother 6400 IU/d + infant 0 IU/d	≥80% in mothers; as low as 61% for infants	78% white; 11% black; 11% Hispanic
Marya 1988[37] India (28ºN) [3243609]	• Health status • Mean age (range/SD), y • Male (%)	no pregnancy-related complications 24 0	Expectant mother's dietary Vit D 35 IU/d; calcium 429 mg/d	Mother Vit D 1.2 mil IU (total; 600,000 IU vit D_2 in 7th & 8th mo) vs. no supplement	nd	
Mallet 1986[40] France (48º N) [3755517]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy newborn nd	Ca intake 550 to 1000 mg/d in 55% of the subjects	Vit D 1000 IU/d vs. 200,000 IU 1x dose	nd	
Nonrandomized comparative study						
Marya 1981[41] India (28ºN) [7239350]	• Health status • Mean age (range/SD), y • Male (%)	no pregnancy-related complications nd 0	Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d	Vit D 1200 IU/d + Ca 375 mg/d (3rd trimester) or Vit D 1.2 mil IU (total; 600,000 IU in 7th & 8th mo) or no supplement	nd	

Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Morley 2006[43] Australia (38ºS) [16352684]	• Health status • Mean age (range/SD), y • Male (%)	singleton pregnancy; no disease 29 0	• Assay method • Season blood drawn	RIA winter & summer	Length and weight in offspring stratified by mother's 25(OH)D		X	X		X	X	99% white; excluded dark skin or women with concealing clothing
Gale 2008[42] PAHSG UK (50ºN) [17311057]	• Health status • Mean age (range/SD), y • Male (%)	singleton pregnancy <17 wk 26.3 0	• Assay method • Season blood drawn	RIA nd	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only

Table 6. Vitamin D and growth outcomes: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Maxwell 1981[38] Brooke 1980[34] [6793058] [6989438]	Pregnant women & infant 0-6 mo (Asians)	Infant birth weight	2°	until delivery	Vit D 1000 IU	59	g	NA	Final 3157	3037, 3277	Diff +123	-50, 296[C]	NS	B
					Control	67		NA	3034	2909, 3159				
		Infant birth length	2°	until delivery	Vit D 1000 IU	59	cm	NA	Final 49.7	49.6, 49.8	Diff +0.2	0.1, 0.3[C]	NS	
					Control	67		NA	49.5	49.4, 49.6				
Feliciano 1994[36] [8078115]	0-6 mo	Weight gain born in spring, N. China[A]	1°	6 mo	Vit D 400 IU	12	g	nd	3745	2613, 4877	-463	-1852, 926[C]	NS	C
					Vit D 200 IU	13		nd	5296	4718, 5874	1088	96, 2080[C]	NS	
					Vit D 100 IU	17		nd	4208	3402, 5013				
		Length gain born in spring, N. China	1°	6 mo	Vit D 400 IU	12	cm	nd	18.8	17.4, 20.2	-0.5	-2.7, 1.7[C]	NS	
					Vit D 200 IU	13		nd	19.0	18.1, 19.9	-0.3	-2.2, 1.6[C]	NS	
					Vit D 100 IU	15		nd	19.3	17.6, 21.0				
El-Hajj 2006[35] [16278262]	9-18 y female, premenarche	Height	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	5.6%	~4.8, 6.4[C]	~1.8%	~0.6, 3.0[C]	0.07	C
					Vit D_3 200 IU			nd	5.0%	~4.2, 5.8[C]	~1.2%	~-0.01, 2.4[C]		
					Placebo			nd	3.8%	~0.9, 6.7[C]				
		Weight	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	18.4%	~14.7, 22.1[C]	~3.5%	~-1.3, 8.3[C]	0.25	
					Vit D_3 200 IU			nd	15.3%	~12.5, 18.1[C]	~0.4	-3.7, 4.5[C]		
					Placebo			nd	14.9%	~11.8, 18.0[C]				
Wagner 2006[39] [17661565]	Lactating mothers & infant 0 - 6 mo; 7 mo - 2 y	Infant weight[B]	1°	7 mo	Mother (400) +infant (300)	10	g	NA	Final 7600	7100, 8100	Diff -800	-2300, 700[C]	0.30	C
					Mother (6400) +infant (0)	9		NA	8400	7700, 9100				
		Infant length	1°	7 mo	Mother (400) +infant (300)	10	cm	NA	Final 65.5	64.4, 66.6	Diff -3.8	-7.8, 0.2[C]	0.06	
					Mother (6400) +infant (0)	9		NA	69.3	67.4, 71.2				
Marya 1988[37] India [3243609]	Pregnant women & infant 0-6 mo	Birth weight	1º	Delivery	Vit D 1.2 mil IU total	100	g	NA	Final 2990	2920, 3060	Diff +190	90, 290[C]	<0.001	C
					No supplement	100		NA	2800	2730, 2870				
		Birth length	2º		Vit D 1.2 mil IU total	100	cm	NA	Final 50.06	49.7, 50.4	Diff +1.6	1.1, 2.1[C]	<0.001	
					No supplement	100		NA	48.45	48.1, 48.8				
Marya 1981[41] [7239350][E]	Pregnant women & infant 0-6 mo	Birth weight	2º	Delivery	Vit D 1.2 mil IU total	20	g	NA	Final 3140	2940, 3340	Diff +410	166, 654[C]	0.001	C
					Vit D 1200 IU + 375 mg Ca (3rd trimester)	25	g	NA	Final 2890	2760, 3020	Diff +160	0, 320[C]	0.05	
					No supplement	75		NA	2730	2650, 2810				

Continued

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Mallet 1986[40] France (48º N) [3755517]	Pregnant women & infant 0-6 mo	Birth weight	2°	delivery	Vit D 1000 IU	21[D]	g	NA	Final 3370 (80)		Diff +160		NS	C
					Vit D 200,000 IU 1x dose	27[D]		NA	3210 (90)					

[A] See Table 1 in original paper for complete results stratified by North vs. South China and birth in spring vs. fall
[B] See Table 3 in original paper for results on 1 mo and 4 mo
[C] Estimated from available data
[D] Estimated from number of mothers; number of infants not reported
[E] This is not an RCT; the supplemented groups were randomized, but not the control (non-supplemented group); data from comparisons between the supplemented groups not reported.

Table 7. Vitamin D and growth outcomes: Results of cohort studies

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D concentration, nmol/L	No. in Category	Final value	Final SD	P value	Study Quality
Morley 2006[43] Australia [16352684]	Pregnant women; infant 0-6 mo	Birth weight (N=374)	Delivery	<28 at 28-32 wk	27	3397 g	57	NS	B
				≥28 at 28-32 wk	347	3555	52		
		Birth length (N=374)	Delivery	<28 at 28-32 wk	27	49.8 cm	2.7	NS	
				≥28 at 28-32 wk	347	50.4	2.4		
Gale 2008[42] PAHSG, UK [17311057]	Pregnant women; infant 0-6 mo	Birth weight (N=466)	Delivery	<30 (Quartile)	nd	3.38 kg	0.46	0.25[A]	C
				30-50	nd	3.40	0.56		
				50-75	nd	3.49	1.57		
				>75	nd	3.43	0.51		
		Weight at 9 mo (N=440)	9 mo	<30	nd	15.9	1.14	0.58	
				30-50	nd	15.8	1.26		
				50-75	nd	16.1	1.34		
				>75	nd	15.9	1.09		
		Weight at 9 y (N=178)	9 y	<30	nd	27.4 kg	1.19	0.10	
				30-50	nd	29.4	1.21		
				50-75	nd	30	1.20		
				>75	nd	29.3	1.19		
	Pregnant women; infant 0-6 mo	Birth length (N=466)	Delivery	<30	nd	50 cm	1.83	0.15	
				30-50	nd	50	2.29		
				50-75	nd	50.5	2.25		
				>75	nd	50.1	2.09		
		Length at 9 mo (N=440)	9 mo	<30	nd	71.2 cm	2.85	0.86	
				30-50	nd	71.4	2.60		
				50-75	nd	71.7	2.89		
				>75	nd	71.1	2.67		
		Height at 9 y (N=178)	9 y	<30	nd	129.6 cm	5.88	0.19	
				30-50	nd	131.5	6.66		
				50-75	nd	131.8	5.09		
				>75	nd	130.6	6.45		

[A] Non-adjusted

Vitamin D and Cardiovascular Disease

Synopsis.

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and incidence of hypertension. One RCT of almost 2700 elderly British who received either vitamin D_3 100,000 IU every 4 months or placebo for 5 years found no statistically significant difference in event rates for various cardiovascular outcomes, including total events and cardiovascular deaths. No effects were also found in subgroup analyses of men and women. Three cohort and one nested case-control studies have analyzed the association between serum 25(OH)D concentrations and cardiovascular outcomes (cardiovascular events, nonfatal myocardial infarction or fatal coronary heart disease, cardiovascular death, myocardial infarction, and stroke). Significant associations were found between progressively lower 25(OH)D concentration and progressively increased risk of cardiovascular events in two studies of people approximately 40 to 75 years old. No significant associations were found between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke in one study each.

Detailed presentation (Tables 8, 9, 10 & 11; Figure 6).

Total cardiovascular events.

Total cardiovascular events were evaluated by an RCT,[44] the Framingham Offspring Study (FOS),[45] and a nested case-control study derived from the Health Professionals Follow-up Study (HPFS).[46] The RCT found no significant effect of vitamin D; both cohort studies found significant associations between lower serum 25(OH)D concentrations and increased rates of outcomes.

The RCT randomized almost 2700 elderly participants (65-85 years) from the general population in Ipswich, UK (52° N) to vitamin D_3 100,000 IU every 4 months or placebo.[44] After 5 years, 36 percent of the participants had a cardiac or cerebrovascular event, but there was no statistically significant difference between those taking vitamin D or placebo. Similar results were found in subgroups of men and women. The RCT was rated quality B primarily due to inadequate verification of outcomes.

The FOS cohort evaluated 1739 men and women with no history of cardiovascular disease and a mean age of 59 years (based on the standard deviation, with an approximate rage of 41 to 77 years).[45] After 5.4 years, 6.9 percent had a cardiovascular event (including myocardial infarction, coronary insufficiency, angina, stroke, transient ischemic attack, claudication, and heart failure). Overall, the methodological quality of the study was A; though their secondary analysis of three categories of serum 25(OH)D concentrations (as opposed to two categories) was rated C due to incomplete reporting and lack of adjustment for important variables including season of blood draw. In their primary analysis, people with serum 25(OH)D concentrations less than 37.5 nmol/L were 70 percent more likely (P=0.02) to have a cardiovascular event. In their secondary analysis, those with 25(OH)D concentrations between 25 and 37.5 nmol/L were about 50 percent more likely (P=0.01) to have an event than those with higher concentrations. Furthermore, a multivariable analysis of continuous 25(OH)D concentrations suggested increased likelihoods of cardiovascular events in those with 25(OH)D concentrations below approximately 50 to 55 nmol/L.

In a nested case-control study of the HPFS, 454 men 40 to 75 years old with no cardiovascular history who had a nonfatal myocardial infarction or coronary heart disease death over a 10 year period were matched with 1354 controls.[46] The methodological quality of the analysis was A, although due to limitations on analyzable serum, the investigators had to use a case-control analysis instead of a complete analysis of all eligible men in the HPFS. Across four categories of men based on their serum 25(OH)D concentrations, lower concentrations were significantly associated with increased cardiovascular events (trend across categories P=0.02). Compared with men who had 25(OH)D concentrations above 75 nmol/L, those with 25(OH)D concentrations 56 to 75 nmol/L had an adjusted relative risk (RR) of 1.6 (95 percent CI 1.1, 2.3), those with 25(OH)D 37.5 to 56 nmol/L had an RR of 1.4 (95 percent CI 0.96, 2.1), and those with 25(OH)D below 37.5 nmol/L had an RR of 2.1 (95 percent CI 1.2, 3.5).

Cardiovascular death.

The British RCT of vitamin $D_3$100,000 IU every 4 months versus placebo analyzed cardiovascular death as a primary outcome; 8 percent of the participants had cardiovascular deaths within 5 years.[44] Fewer people taking vitamin D_3 supplements had cardiovascular deaths (RR = 0.84), but this finding was not statistically significant (95 percent CI 0.65, 1.10). Similar results were found in subgroups of men and women.

An analysis of NHANES III (methodological quality C) evaluated cardiovascular death (due to hypertensive disease, ischemic heart disease, arrhythmia, heart failure, cerebrovascular disease, atherosclerosis or other disease of the arteries) in over 13,000 men and women regardless of baseline medical history.[47] During almost 9 years of followup, 5.8 percent had a cardiovascular death. The analysis compared four categories of serum 25(OH)D concentrations ranging from less than 44.5 nmol/L to more than 80 nmol/L. No significant association was found between serum 25(OH)D concentration and cardiovascular death.

Ischemic heart disease.

The RCT evaluated total ischemic heart disease.[44] In this elderly British population, 17 percent had an ischemic heart disease event; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Ischemic heart disease death.

The RCT evaluated total ischemic heart disease death as a primary outcome.[44] In the trial, 3.4 percent had an ischemic heart disease event; no effect of vitamin D_3 supplementation was found (RR = 0.84 [95 percent CI 0.56, 1.27]). Similar results were found in subgroups of men and women.

Myocardial infarction.

In one small analysis, 755 elderly (age 65 to 99 years) Finnish men and women, regardless of cardiovascular history, were evaluated on the basis of myocardial infarction (methodological quality C due to lack of reporting of relevant data including information on the serum 25(OH)D or $1,25(OH)_2D$ concentrations within the tertiles).[48]
During 10 years of followup, 17 percent of the participants had a myocardial infarction. Both analyses of serum 25(OH)D and $1,25(OH)_2D$ concentrations found no significant association with risk of myocardial infarction.

Stroke.

The RCT evaluated total cerebrovascular disease.[44] In this elderly British population, 7.7 percent had a cerebrovascular event; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Stroke was evaluated in the same small Finnish study. During 10 years of followup, 9.3 percent of the participants had a stroke. Both analyses of serum 25(OH)D and $1,25(OH)_2D$ concentrations found no significant association with risk of stroke.

Cerebrovascular death.

The RCT evaluated cerebrovascular disease death as a primary outcome.[44] In the trial, 2.0 percent had a fatal stroke; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Findings per vitamin D concentration.

The RCT compared vitamin D_3 supplementation 100,000 IU every 4 months with placebo, but found no effect on cardiovascular outcomes. Two cohort studies found a significant association between higher serum 25(OH)D concentrations and lower risk of combined cardiovascular events. Both found that those people in the highest 25(OH)D category analyzed within each study had the lowest risk. The FOS used a maximum threshold of 37.5 nmol/L; the HPFS used a maximum threshold of 75 nmol/L. The FOS provided a graphic representation of a multivariable regression of continuous 25(OH)D concentrations (Figure 2 in the study).[45] The risk of cardiovascular events rose below 37 to 50 nmol/L serum 25(OH)D concentration. The Finnish cohort did not report the range of serum 25(OH)D and $1,25(OH)_2D$ concentrations.[48]

Findings per age and sex.

The single RCT included elderly people from the general population. No effects on various cardiovascular events were found. Subgroup analyses of men and women yielded similar findings. The four cohort studies included adults across the full age range. Three of the cohorts included about half men and women; one included only men. None evaluated potential differences in associations based on age or sex, but no differences were evident across studies.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** For cardiovascular events, only a minority of evaluated participants were within this life stage (almost all above 40 years). The NHANES III study, which found no association between serum 25(OH)D concentration and cardiovascular death, included largely people within this life stage.
- **51 – 70 y** The majority of people investigated for the association between serum 25(OH)D concentration and cardiovascular events were within this life stage. Significant associations were found between lower serum 25(OH)D concentrations and increased rates of cardiovascular events, across a range of 25(OH)D concentrations. The NHANES III study likely included many people within this life stage; no association was found with cardiovascular death.
- **≥71 y** The majority of participants in the British RCT included men and women within this age group. Vitamin D supplementation was not found to have an effect on

- **Postmenopause** Only the RCT provided data on a subgroup that included only postmenopausal women. No effect of vitamin D_3 supplementation was found.
- **Pregnant & lactating women** Not reviewed

Table 8. Vitamin D and cardiovascular outcomes: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 200[44] Ipswich, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65-85) 76%	742 mg/day (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs placebo every 4 months	76% with at least 80% compliance; 66% at last dose (80% if excluding deaths)	

Table 9. Vitamin D and cardiovascular outcomes: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex (Subgp)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 200[44] [12609940]	65-85 y, Both	CVD, total	2°	5 y	Vit D_3 100,000 IU every 4 mo	477	1345	Age adj RR (Vit D/Placebo)	0.90[A]	0.77, 1.06	0.22	B
					Placebo	503	1341					
		IHD, total	2°		Vit D_3	224	1345	Age adj RR (Vit D/Placebo)	0.94[A]	0.77, 1.15	0.57	
					Placebo	233	1341					
		CeVD, total	2°		Vit D_3	105	1345	Age adj RR (Vit D/Placebo)	1.02[A]	0.77, 1.36	0.87	
					Placebo	101	1341					
		CVD death	1°		Vit D_3	101	1345	Age adj RR (Vit D/Placebo)	0.84[A]	0.65, 1.10	0.20	
					Placebo	117	1341					
		IHD death	1°		Vit D_3	42	1345	Age adj RR (Vit D/Placebo)	0.84[A]	0.56, 1.27	0.41	
					Placebo	49	1341					
		CeVD death	1°		Vit D_3	28	1345	Age adj RR (Vit D/Placebo)	1.04[A]	0.61, 1.20	0.89	
					Placebo	26	1341					

[A] Similar results for subgroups of men and women

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Wang 2008[45] Framingham Offspring Framingham, MA (mostly) (42°N) [18180395]	• Health status • Mean age (SD), y • Male (%)	No CVD 59 (9) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Outcome stratified by 2 or 3 categories	X[A]	X	X	X	X[A]	X	CVD event
Giovannucci 2008[46] HPFS US (various) [18541825]	• Health status • Mean age (range), y • Male (%)	No CVD 64 (40-75) 100	• Dietary assessment method • Internal validation? (y/n)	RIA (Hollis 1993) All	Outcome stratified by 4 categories[B]	X	X	X	X	X	X	Nonfatal MI or fatal CHD
Melamed 2008[47] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	Any 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All (even distribution)	Outcome stratified by 4 categories	X	X	X	X	X	X	CVD death
Marniemi 2005[48] Turku, Finland (60°N) [15955467]	• Health status • Mean age (range), y • Male (%)	Any 79 (65-99) 48	• Assay method • Season blood drawn	RIA (Incstar) All	Outcome stratified by tertiles		X				X	MI Stroke

[A] Not in 3-category analysis
[B] Case-control study

Table 11. Vitamin D and cardiovascular outcomes: Results of cohort studies

Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
CVD Events											
Both Sexes											
Wang 2008[45] Framingham Offspring [18180395]	Mean (SD) 59 (9), Both	CVD event (120/1739; 0.069)	5.4 y	25(OH)D	<37.5	50	481	1.70	1.08, 2.67*	0.02[A]	A
					≥37.5	70	1258	**1**	**Reference**		
					<25	nd	nd	1.80	1.05, 3.08*	0.01	C
					25-37.5	nd	nd	1.53	1.00, 2.36*		
					≥37.5	70	1258	**1**	**Reference**		
Men											
Giovannucci 2008[46] HPFS [18541825]	40-75 y, Men	Nonfatal MI or fatal CHD (454 cases; 1354 controls)	10 y	25(OH)D	≤37.5	63	150	2.09	1.24, 3.54	0.02[BC]	A
					37.5-56.25	156	463	1.43	0.96, 2.13		
					56.25-75	165	464	1.60	1.10, 2.32		
					>75	70	277	**1**	**Reference**		
CVD Death											
Both Sexes											
Melamed 2008[47] NHANES III [18695076]	≥20 y, Both	CVD death (777/13,331; 0.058)	8.7 y	25(OH)D	<44.5	nd	nd	1.20	0.87, 1.64	nd	C
					44.5-60.75	nd	nd	0.88	0.69, 1.14		
					60.75-80.25	nd	nd	0.83	0.65, 1.07		
					>80.25	nd	nd	**1**	**Reference**		
Myocardial Infarction											
Both Sexes											
Marniemi 2005[48] [15955467]	65-99 y, Both	MI (130/755; 0.172)	10 y	25(OH)D	nd	nd	~252	**1**	**Reference**	nd	C
					nd	nd	~252	0.99	0.64, 1.53		
					nd	nd	~252	0.77	0.47, 1.27		
				$1,25(OH)_2D$	nd	nd	~252	**1**	**Reference**	nd	
					nd	nd	~252	1.05	0.68, 1.62		
					nd	nd	~252	0.82	0.52, 1.30		

Continued

Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Stroke											
Both Sexes											
Marniemi 2005[48] [15955467]	65-99 y, Both	Stroke (70/755; 0.093)	10 y	25(OH)D	nd	nd	~252	**1**	**Reference**	nd	C
					nd	nd	~252	1.13	0.62, 2.05		
					nd	nd	~252	1.00	0.51, 1.94		
				$1,25(OH)_2D$	nd	nd	~252	**1**	**Reference**	nd	
					nd	nd	~252	0.63	0.37, 1.09		
					nd	nd	~252	0.41	0.22, 0.77*		

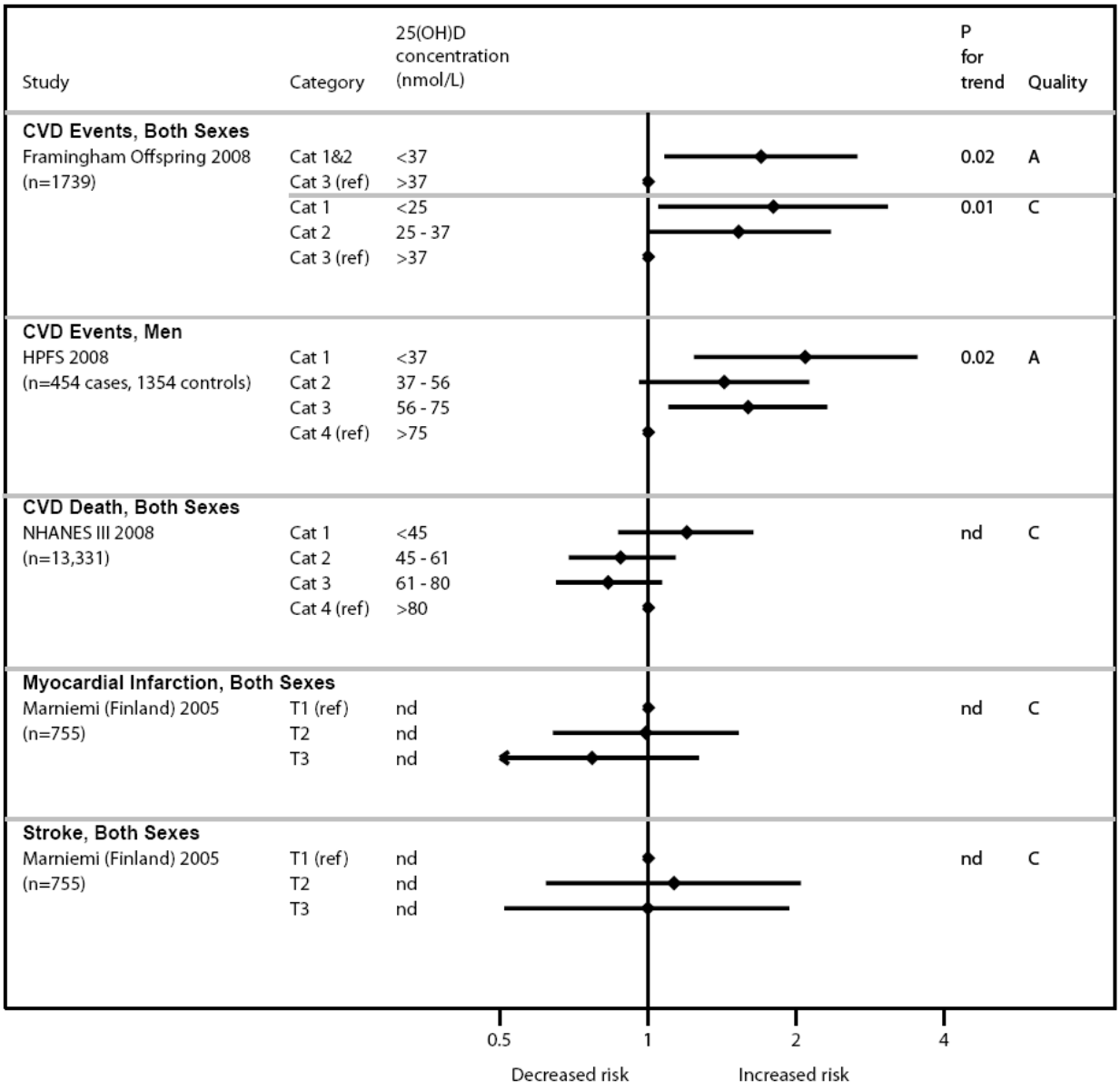
* Statistically significant (P<0.05)

[A] Multivariable Cox regression with continuous 25(OH)D and regression splines with nonlinear relationships suggests an increased hazard of CVD events at serum 25(OH)D concentrations below approximately 50-55 nmol/L. See Figure 2 on page 508 of article.

[B] Adjusted regression analyses found OR=0.98 (0.96, 0.998) per 2.5 nmol/L increase in 25(OH)D and risk reduction of -2.1% (-0.2%, -4.0%) per 2.5 nmol/L increase in serum 25(OH)D concentration.

[C] In a subgroup analysis of participants on no cholesterol lowering drugs at baseline, comparing the highest serum 25(OH)D concentration category (>75 nmol/L) to the lowest (≤37.5 nmol/L), adjusted RR=2.30 (1.33, 3.97).

Figure 6. Cardiovascular outcomes risk stratified by vitamin D concentration



Vitamin D and Body Weight

We searched for systematic reviews and primary studies that evaluated associations between vitamin D intake or body stores and *incidence of overweight or obesity*; no such studies were found. For the outcome *weight change* (in kilograms or body mass index units), we included only randomized controlled trials. The EPC and the TEP agreed that the limited resources would not be expended on reviewing observational studies for the surrogate outcome body weight (where overweight or obesity are considered to be the clinical outcomes). We included only studies of adults. Studies of weight gain in children are included in the "Growth" section.

Synopsis.

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and body weight in adults. Three RCTs from Finland, Norway, and India compared different doses of vitamin D (300 IU daily, 20,000 or 40,000 IU weekly, or 120,000 IU every 2 weeks) to placebo, with or without supplemental calcium in both groups. The study participants also varied: they were postmenopausal women, obese men and women, or only obese men. In the Finnish and Norwegian studies, the participants on average, gained weight in all groups over 1 or 3 years; in the Indian study weight remained mostly stable over 6 weeks. All studies found no difference in weight change with or without vitamin D supplementation.

Detailed presentation (Tables 12 & 13).

Three RCTs of vitamin D reported body weight (or body mass index [BMI]) as an outcome. The Kuopio (Finland) Osteoporosis Risk Factor and Prevention Study (Kuopio ORFPS) included postmenopausal women in a four-arm study.[49] Two of the study arms included hormone replacement treatment and are not further discussed here. The remaining two arms compared vitamin D_3 300 IU (83 women) versus placebo (95 women), where all women were taking low dose calcium lactate 500 mg/d (equivalent to 93 mg Ca^{++}/d). Women on cholesterol-lowering medication at any point during the trial were excluded. The primary outcome of the trial was the serum lipid profile. The women ranged in age from 47 to 56 years. After 3 years, women, on average, gained weight in both study arms (about 1-2 kg). Those in the placebo arm gained an absolute 1.5 percent more weight than those in the vitamin D arm, but the difference was not statistically significant. The study had a methodological quality of C due to an uneven distribution of body weights between study arms at baseline (means 71.5 and 67.6 kg) and an overall withdrawal rate of over 30 percent.

The second trial was conducted in Norway among healthy overweight and obese women and men.[50] The participants' mean baseline serum 25(OH)D concentration was 53 nmol/L. The trial compared vitamin D_2 40,000 IU weekly (116 participants completed), 20,000 IU weekly (106 participants), and placebo (112 participants). All study participants also took calcium carbonate 500 mg daily. Almost all participants complied with the vitamin D (or placebo). Changes in weight and BMI were primary outcomes. The participants ranged in age from 21 to 70 years. After 1 year, changes in weight were small (increases of 0.1-0.5 kg) in each trial group. Compared to the placebo group, those taking the larger dose of vitamin D had less weight gain than those taking the smaller dose, but none of the differences among study groups were statistically significant. The study was rated methodological quality B, primarily due to the high dropout rate (25 percent), which was not explained.

The third trial was conducted in New Delhi, India among healthy obese men.[51] The participants' mean baseline serum 25(OH)D concentration was about 33 nmol/L. The trial compared vitamin D_3 120,000 given under supervised conditions every 2 weeks and placebo in 100 men, of whom 71 were analyzed; most dropouts occurred because of refusals for subsequent blood draws (to assess the primary outcome). After 6 weeks, weight in kg and BMI were essentially stable, with no difference in weight change between the interventions. The study was rated methodological quality B because of the high dropout rate; for weight (in kg), the study was of quality C because baseline weights were not reported.

Findings per vitamin D dose.

There was a lack of effect found across a range of doses from 300 IU to 8570 IU (prorated) daily.

Findings per age and sex.

There was a lack of effect found in studies both of men mostly in their 40s, somewhat older people of both sexes, and postmenopausal women.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No effect was found in one trial of men mostly within this life stage after 6 weeks.
- **51 – 70 y** The majority of people in the trials were within this life stage. No significant effect was found on weight from vitamin D supplementation for 1 or 3 years.
- **≥71 y** No data
- **Postmenopause** All the women in the Finnish trial were postmenopausal.
- **Pregnant & lactating women** Not reviewed

Table 12. Vitamin D and weight: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Heikkinen 1997[49] Kuopio ORFPS Kuopio, Finland (63°N) [9405029]	• Health status • Mean age (range), y • Male (%)	All, post-menopause 53 (47-56) 0	nd	Vit D_3 & Ca lactate vs Placebo & Ca lactate	nd	
Sneve 2008[50] Tromsø, Norway (70°N) [19056900]	• Health status • Mean age (range), y • Male (%)	Healthy overweight and obese 48 (21-70) 36	25(OH)D 53.1±16.9 nmol/L Ca intake 940±398 mg/d	Vit D_3 40,000 IU per week vs Vit D_3 20,000 IU per week vs Placebo All: Ca carbonate 500 mg/d	The compliance rate for cholecalciferol/placebo capsules were 95% in all 3 groups, and for the calcium tablets 81-85% across all 3 groups.	
Nagpal 2009[51] New Delhi, India (28.5°N) [19125756]	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 44 (8) 100%	25(OH)D: 36.5 nmol/L (treatment group), 30.0 nmol/L (control group)	Vit D_3 120,000 IU every 2 weeks vs Placebo	100% (implied); supervised home visits	Excluded subjects who refused subsequent blood draws

Table 13. Vitamin D and weight: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex (Subgp)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Isocaloric Diet														
Heikkinen 1997[49] Kuopio ORFPS [9405029]	47-56 y, Women	Weight	2°	3 y	Vit D_3 300 IU + Ca lactate 93 mg	83	kg	71.5	+1.84%	+0.43%, +3.25%	-1.5%	-3.6%, +0.6%[A]	NS[B]	C
					Ca lactate 93 mg	95		67.6	+3.32%	+1.73%, 4.91%				
Sneve 2008[50] [19056900]	21-70 y, Both	Weight	1°	1 y	Vit D_3 40,000 IU weekly+ Ca carbonate 500 mg	116	kg	101.0	+0.1	-0.6, +0.8	-0.4	-1.3, +0.5[A]	NS	B
					Vit D_3 20,000 IU weekly + Ca carbonate 500 mg	106		98.6	+0.3	-0.3, +0.9	-0.2	-1.1, +0.7[A]	NS	
					Ca carbonate 500 mg	112		100.6	+0.5	-0.2, +1.2				
		BMI	1°	1 y	Vit D_3 40,000 IU weekly + Ca carbonate 500 mg	116	BMI	35.0	0.0	-0.2, +0.2	-0.2	-0.6, +0.2[A]	NS	
					Vit D_3 20,000 IU weekly + Ca carbonate 500 mg	106		34.4	+0.1	-0.1, +0.3	-0.1	-0.4, +0.2[A]	NS	
					Ca carbonate 500 mg	112		35.1	+0.2	-0.1, +0.5				
Nagpal 2009[51] New Delhi, India [19125756]	44 (8, SD) Men	Weight	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	kg	nd	+0.03	-0.6, +0.6	+0.42	-0.4, +1.2	NS	C
					Placebo	36		nd	-0.38	-0.9, +0.2				
		BMI	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	BMI	26.7	-0.02	-0.2, +0.2	+0.02	-0.3, +0.3	NS	B
					Placebo	36		26.0	-0.04	-0.3, +0.2				

[A] Estimated from reported data
[B] Per estimated 95% confidence interval, P=0.17

Vitamin D and Cancer

Cancer from all causes and total cancer mortality.

Synopsis.

No qualified systematic reviews have evaluated relationships between vitamin D and total cancer incidence or mortality. One RCT showed no effect of combined vitamin D_3 (1000 IU/d) and calcium (~1500 mg/d) supplementation versus calcium supplementation (~1500 mg/d) alone on the risk of total cancer in healthy postmenopausal women (>55 years old) living in Nebraska (latitude 41°N). Another RCT also found no difference in total cancer mortality or incidence between supplemental vitamin D_3 (100,000 IU every 4 months) and placebo in elderly (71+ years old) men and women living in the United Kingdom (latitude 52° N). Both RCTs were rated B quality.

Analyses using NHANES III data (general adult populations living in the US) showed no significant association between baseline 25(OH)D concentrations and total cancer mortality.

Detailed presentation (Tables 14, 15, 16 & 17).

A 4-year population-based RCT,[52] sampled from a 9 county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) or calcium alone (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) compared to placebo in reducing fracture incident. Only the comparison between the combined vitamin D and calcium versus the calcium alone groups is discussed here. The other comparisons are described in the calcium and combined vitamin D and calcium sections. This study was rated methodological quality B. Incidence of cancer was a secondary outcome of this trial. A total of 1179 postmenopausal women, aged more than 55 years old, were randomized. The mean 25(OH)D concentration at baseline was 72 nmol/L. The relative risk of developing cancer at the end of study was 0.76 (95 percent CI: 0.38, 1.55). On the hypothesis that cancers diagnosed early in the study would have been present, although unrecognized on entry, the analyses were restricted to women who were free of cancer at 1 year intervention. The relative risk of developing cancer at the end of study for the vitamin D_3 plus calcium group changed to 0.55 (95 percentCI 0.24, 1.28).

Another 5-year RCT compared the effects of supplemental vitamin D_3 (100,000 IU every 4 months) with placebo on total cancer mortality and incidence in 2686 elderly participants with a mean age of 75 years in the United Kingdom (latitude 52° N).[44] Total cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin D_3 supplementation had no significant effect on the prevention of total cancer mortality (HR 0.86; 95 percent CI 0.61, 1.20) or incidence (HR 1.09; 95 percent CI 0.86, 1.36). This trial was rated B because it did not report in sufficient detail the randomization method, and the outcome ascertainment was based on death certificates or self-reported data, not verified with another objective documents (e.g., medical records or pathology reports).

Reported in two publications (one was rated B and one was rated C), there was no association between baseline 25(OH)D concentrations and total cancer mortality in the total NHANES III study population[47,53] or in subgroup analyses by either season or latitude after a median 9 years of followup.[53]

Findings by age, sex and/or ethnicity.

There were no differences in the total cancer mortality and incidence between men and women, reported in a 5-year RCT compared the effects of supplemental vitamin D_3 (100,000 IU every 4 months) with placebo. In the NHANES III analysis, there was a suggestion of increased risk of total cancer mortality in men whose baseline 25(OH)D were in the two highest categories (80 to <100 nmol/L; ≥100 nmol/L) compared to the reference category (<50 nmol/L) [80 to <100 nmol/L: RR = 1.21, 95 percent CI 0.83 to 1.78; ≥100 nmol/L: RR = 1.35; 95 percent CI 0.78 to 2.31; P for trend=0.08]. However, this relationship was not seen in women (P for trend=0.12).[53] When racial/ethnic groups were considered separately, there was also no association between baseline 25(OH)D concentrations and total cancer mortality in non-Hispanic whites (P for trend=0.80), non-Hispanic blacks (P for trend=0.14), or Mexican Americans (P for trend=0.37).

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** Analyses using NAHANES III data showed no significant association between baseline 25(OH)D concentrations and total cancer mortality. NHANES III included participants mostly within this life stage.
- **51 – 70 y** A proportion of participants in NHANES III were in this life stage, but no unique conclusions are possible for this life stage separate from those for people 19 to 50 years.
- **≥71 y** One RCT included elderly men and women mostly in this life stage. The trial found no difference in total cancer mortality or incidence between supplemental vitamin D_3 (100,000 IU every 4 months) and placebo.
- **Postmenopause** One RCT with healthy postmenopausal women showed no effect of vitamin D_3 supplementation (1000 IU/d) on the risk of total cancer.
- **Pregnant & lactating women** No Data

Table 14. Vitamin D and total cancer: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2007[52] Nebraska, US (41º N) [17556697]	• Health status • Mean age (SD), y • Male (%)	Mentally and physically fit; post-menopause 67 (7.3) 0	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo	nd	
Trivedi 2003[44] Oxford, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65-85) 76%	25(OH)D: 53.4 nmol/L Calcium intake= 742 mg/d (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs placebo every 4 months	Participants taking ≥80% of study medication: 76%[A]	Previous CVD: 28%, previous cancer: 6%, steroids user: 5%, and HRT taker: 7%

[A] No difference between the vitamin D and the placebo arm.

Table 15. Vitamin D and total cancer: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Freedman 2007[53] NHANES III US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Any 44 (≥17) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by prespecified baseline 25(OH)D cut points	X	X	X	X	X	X	Final model includes sex, race/ethnicity, and smoking pattern. Other potential confounders were examined but not chosen.
Melamed 2008[47] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	

Table 16. Vitamin D and total cancer: Results of RCTs

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lappe 2007[52] Nebraska, US (41º N) [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	13	446	RR (Vit D+Ca vs Ca)	0.76	0.38, 1.55	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	17	445					
	Post-menopausal women	Incident cancer (restricted to subjects who were free of cancer at 1 y intervention)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	8	403	RR (Vit D+Ca vs Ca)	0.55	0.24,1.28	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	15	416					
Trivedi 2003[44] [12609940]	65-85 y, Both sexes	Incident cancer (all causes)	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	188	1345	HR (Vit D vs placebo)	1.09	0.86, 1.36	NS	B
					Placebo	173	1341					
		Total cancer mortality	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	63	1345	HR (Vit D vs placebo)	0.86	0.61, 1.2	NS	
					Placebo	72	1341					

Table 17. Vitamin D and total cancer: Results of cohort studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Freedman 2007[53] NHANES III US [16481636]	Adults, both sexes	Cancer mortality (536/16818; 0.032)	105 mo	<50	175	5744	**1**	**Reference**	0.65	B
				50 to <62.5	103	3143	1.22	0.91, 1.64		
				62.5 to <80	117	3713	1.02	0.69, 1.50		
				80 to <100	80	4218 (total, ≥80 nmol/L)	1.00	0.71, 1.40		
				100 to <120	41		0.92	0.58, 1.46		
				≥120	20		1.49	0.85, 2.64		
	Adults, males	Cancer mortality (318/7632; 0.042)	105 mo	<50	88	1993	**1**	**Reference**	0.08	
				50 to <62.5	57	1461	1.03	0.73, 1.44		
				62.5 to <80	71	1845	0.99	0.57, 1.74		
				80 to <100	58	2333 (total, ≥80 nmol/L)	1.21	0.83, 1.78		
				≥100	44		1.35	0.78, 2.31		
	Adults, females	Cancer mortality (218/9163; 0.024)	105 mo	<50	87	3751	**1**	**Reference**	0.12	
				50 to <62.5	46	1682	1.40	0.94, 2.08		
				62.5 to <80	46	1845	1.02	0.62, 1.67		
				80 to <100	22	1885 (total, ≥80 nmol/L)	0.72	0.40, 1.26		
				≥100	17		0.78	0.40, 1.53		
Melamed 2008[47] NHANES III US (various) [18695076]	Adults, both sexes	Cancer mortality (N=13331)	Median 8.7 (IQR 7.1-10.2) y	>80	nd	nd	**1**	**Reference**	nd	C
				61-80	nd	nd	0.8	0.54, 1.19		
				44-60	nd	nd	1.08	0.8, 1.46		
				<44	nd	nd	0.91	0.63, 1.31		

* Statistically significant (P<0.05)

Prostate cancer.

Synopsis.

No qualified systematic reviews have evaluated the association between serum vitamin D concentrations and incidence of prostate cancer. Eight nested case-control studies (2B, 6C) found no association between baseline serum 25(OH)D concentrations and the risk of prostate cancer. One study rated C found a significant association between lower baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and higher risk of prostate cancer (adjusted OR 1.8, lowest compared to highest quartile). The same study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and who had serum 25(OH)D concentration less than 40 nmol/L (adjusted OR 3.5). However, there was no difference in risk between low and high serum 25(OH)D concentration for those older than 51 years at study entry. A C study suggested an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.

Detailed presentation (Tables 18 & 19; Figure 7).

A total of 12 nested case-control studies in 14 publications reported on the association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.[53-66] The number of cases ranged from 61 to 749. The latitudes of the studies ranged from 21º N to 60º N. The mean age of the subjects ranged from 44 to 68 years. Baseline serum concentrations of 25(OH)D in these studies ranged from 12.8 to 194 nmol/L. The time between blood drawn and the diagnosis of prostate cancer varied from 2 to 16 years. The methodological quality of three studies was rated B and nine studies were rated C.

19-50 years.

Two studies provided data on younger subjects. Ahonen et al. analyzed subjects from 40 to 57 years of age.[55] The study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95% CI 1.7, 7.0). The corresponding adjusted OR for those older than 51 years at study entry was 1.2 and was not significant. This study adjusted for factors related to insulin resistance syndrome but not those potentially related to prostate cancer.

Freedman et al. analyzed data from NHANES III and reported on subjects with a mean age of 44 years and found that the adjusted relative risk of mortality from prostate cancer was 0.91 (95% CI 0.39, 2.14) in the group with baseline serum 25(OH)D concentration of at least 62.5 nmol/L compared to the group with less than 62.5 nmol/L.[53]

51-70 years.

Ten studies reported data on subjects with a mean age ranged from 51 to 68 years. Eight studies did not find an association by trend analysis between baseline serum 25(OH)D concentrations and the risk of prostate cancer.[54,56-63,66] One study found no association between baseline serum 25(OH)D concentrations and mortality from prostate cancer.[58] One study found an association between lower baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and the risk of prostate cancer (P for trend = 0.01).[55] The adjusted OR of the lowest compared to highest quartile was 1.8. The study also found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95 percent CI 1.7, 7.0). However, there was no difference in risk (adjusted OR 1.2, P=NS) between low (≤40 nmol/L) and high (>40 nmol/L) serum 25(OH)D

concentration for those older than 51 years at study entry. This study did not adjust for factors potentially relevant to prostate cancer. One study reported an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer: the odds ratio in the group with 25(OH)D concentration of at least 80 nmol/L was 1.7 (95 percent CI 1.1, 2.4) compared to the group with a 25(OH)D concentration of 40-49 nmol/L; the odds ratio in the group with 25(OH)D concentration of no more than 19 nmol/L was 1.5 (95 percent CI 0.8, 2.7) compared to the group with a 25(OH)D concentration of 40 to 49 nmol/L.[64] Even though this study used a conditional logistic regression in its analysis to maintain matching status, it was unclear if additional factors potentially relevant to prostate cancer were also entered into the regression analysis.

1,25(OH)$_2$D.

Five studies reported on the association between 1,25(OH)$_2$D serum concentrations and the risk of prostate cancer. Four studies did not find an association.[59,62,63,66] One study found that the risk of prostate cancer decreased with higher serum concentrations of 1,25(OH)$_2$D in men with low serum concentrations of 25(OH)D (unadjusted OR 0.15, comparing 4th quartile of 1,25(OH)$_2$D (104-211 pmol/L) to 1st quartile (13-68 pmol/L) in men with serum 25(OH)D concentrations that ranged from 7.5-45 nmol/L).[58] When stratified by age and race, this association was only found in men above the median age of 57 years at time of blood drawn but not in younger men; the association was similar in black and white men.

Findings by life stage.

- **0 – 6 mo** not applicable
- **7 mo – 2 y** not applicable
- **3 – 8 y** not applicable
- **9 – 18 y** not reviewed
- **19 – 50 y** One study found that the prostate cancer risk was highest in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95 percent CI 1.7, 7.0). Another study analyzed data from NHANES III and reported on subjects with a mean age of 44 years and found that the adjusted relative risk of mortality from prostate cancer was 0.91 (95 percent CI 0.39, 2.14) in the group with baseline serum 25(OH)D concentration of at least 62.5 nmol/L compared to the group with less than 62.5 nmol/L.
- **51 – 70 y** Eight studies did not find an association by P for trend analysis between baseline serum 25(OH)D concentrations and the risk of prostate cancer. One study found an inverse association of baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and the risk of prostate cancer (adjusted OR 1.8, lowest compared to highest quartile, P for trend = 0.01). This study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95 percent CI 1.7, 7.0). However, there was no difference in risk (adjusted OR 1.2, P=NS) between low (≤40 nmol/L) and high (>40 nmol/L) serum 25(OH)D concentration for those older than 51 years at study entry. One study reported an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer: the odds ratio in the group with 25(OH)D concentration of at least 80 nmol/L was 1.7 (95 percent CI 1.1, 2.4) compared to the group with a 25(OH)D concentration of 40-49 nmol/L; the odds ratio in the group with 25(OH)D

concentration of no more than 19 nmol/L was 1.5 (95 percent CI 0.8, 2.7) compared to the group with a 25(OH)D concentration of 40 to 49 nmol/L.

- **≥71 y** No study specifically targeted men older than 70 years.
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Not applicable

Table 18. Vitamin D and prostate cancer: Characteristics of nested case-control studies

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
Ahn 2008[54] PLCO US (21ºN to 44ºN) [18505967]	Health status Mean age (range/SD), y Male (%)	8% current smoker 67.8 (5.3) 100	Assay Season blood drawn	RIA (Heartland) nd	Prostate cancer risk stratified by baseline 25(OH)D quintiles	X		X	X		X	
Platz 2004[63] Mikhak 2007[61] HPFS US (multiple latitudes) [15090720] [17440943]	Health status Mean age (range/SD), y Male (%)	Smoked 18%; DM 3.6% 66 (7) 100	Assay Season blood drawn	RIA nd	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	6% nonwhite
Freedman 2007[53] NHANES III US (multiple latitudes) [17971526]	Health status Mean age (range/SD), y Male (%)	28% current smoker 44 100	Assay Season blood drawn	RIA South: Nov to Mar; North: Apr to Oct	Prostate cancer mortality stratified by 2 baseline 25(OH)D categories	X	X	X	X	X	X	71% white; 14% black; 6% Hispanics
Tuohimaa 2004[64] Helsinki Heart Vasterbotten; Janus Project; Finland (60°N) [14618623]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects <40 to >60 100	Assay Season blood drawn	RIA (Incstar) nd	Prostate cancer risk stratified by 5 baseline 25(OH)D categories		X			X		
Li 2007[60] Gann 1996[66] PHS US (multiple latitudes) [17388667] [8850273]	Health status Mean age (range/SD), y Male (%)	on ASA, β-carotene, placebo trial; 9% current smoker 58.9 (8.3) 100	Assay Season blood drawn	RIA (Bruce Hollis) 24% spring or winter	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X				X	94% white
Corder 1993[58] San Francisco US	Health status Mean age (range/SD), y	nd 57 (38-81)	Assay	Competitive protein-binding (Haddad, 1971)	Prostate cancer risk compared by baseline 25(OH)D		X			X		50% black; 50% white

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
(37ºN) [8220092]	Male (%)	100	Season blood drawn	nd								
continued												
Ahonen 2000[55] Helsinki Heart Finland (60°N) [11075874]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 40-57 100	Assay Season blood drawn	RIA (Incstar) Jan-Feb; Mar-May; Sep	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X	X	X	X	
Nomura 1998[62] Honolulu Heart US (21ºN) [9794175]	Health status Mean age (range/SD), y Male (%)	64% smoked 58 (49-70) 100	Assay Season blood drawn	Protein-binding nd	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	100% Japanese Americans
Tuohimaa 2007[65] Helsinki Heart Finland (60°N) 17301263	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 51 (3.7) 100	Assay Season blood drawn	RIA (Incstar) Most in winter	Prostate cancer risk stratified by 3 baseline 25(OH)D categories		X	X	X			
Jacobs 2004[59] NPC Eastern US (25º46'N to 41ºN) [15225833]	Health status Mean age (range/SD), y Male (%)	Selenium vs. placebo subjects[A] 68 (nd) 100	Assay Season blood drawn	RIA nd	Prostate cancer risk stratified by baseline 25(OH)D tertiles		X	X	X	X	X	
Braun 1995[57] WCC, MD US (39°N) [7612803]	Health status Mean age (range/SD), y Male (%)	nd <45-75+ 100	Assay Season blood drawn	RIA (Bruce Hollis, 1993) Aug through Nov	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X					100% white
Baron 2005[56] CPP US (multiple latitudes) [15767334][B]	Health status Mean age (range/SD), y Male (%)	had >1 colon adenoma removal 62 (8.7) 100	Assay Season blood drawn	Competitive protein-binding (Quest) nd	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X		5% black
continued												

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
Braun 1995[57] WCC, MD US (39°N) [7612803]	Health status Mean age (range/SD), y Male (%)	nd <45-75+ 100	Assay Season blood drawn	RIA (Bruce Hollis, 1993) Aug through Nov	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X					100% white
Baron 2005[56] CPP US (multiple latitudes) [15767334][B]	Health status Mean age (range/SD), y Male (%)	had >1 colon adenoma removal 62 (8.7) 100	Assay Season blood drawn	Competitive protein-binding (Quest) nd	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X		5% black

[A] For prevention of recurrence of non-melanoma skin cancer
[B] This is a cohort study, not a nested case-control study.

Table 19. Vitamin D and prostate cancer: Results of nested case-control studies

Author Year Study Name PMID	Life Stage (male), y	Outcome (no. of cases; no. of control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of cases	No. of control	Adjusted OR	95% CI	P for trend	Study Quality
Ahn 2008[54] PLCO [8505967]	51-70	Prostate cancer (741; 781)	2-8	12.8-42.5	119	157	**1**	**Reference**	0.20	B
				42.5-51.	125	156	1.10	0.78, 1.56		
				51.4-60.5	190	157	1.53	1.10, 2.13*		
				60.6-71.7	167	156	1.33	0.95, 1.86		
				71.8-129.5	148	155	1.18	0.83, 1.68		
Platz 2004[63] Mikhak 2007[61] HPFS [15090720] [17440943]	51-70	Prostate cancer (460; 460)	2.2 (mean)	Quartile 1[A]	109	114	**1**	**Reference**	0.59	B
				Quartile 2	115	113	1.00	0.67, 1.49		
				Quartile 3	94	120	0.77	0.51, 1.15		
				Quartile 4	142	113	1.19	0.79, 1.79		
Freedman 2007[53] NHANES III [17971526]	19-50	Mortality prostate cancer	nd	<62.5	22	nd	**1**	**Reference**	0.95	B
				≥62.5	25	nd	0.91	0.39, 2.14		
Tuohimaa 2004[64] Helsinki Heart [14618623]	19-50 51-70	Prostate cancer (622; 1451)	≤9 ->14 (range)	≤19	19	nd	1.5	0.8, 2.7		C
				20-39	169	nd	1.3	0.98, 1.6		
				40-59	229	nd	**1**	**Reference**		
				60-79	138	nd	1.2	0.9, 1.5		
				≥80	67	nd	1.7	1.1, 2.4*		
Li 2007[60] PHS [17388667]	19-50 51-70	Prostate cancer (492; 664)	11 (median)	Quartile 1[B]	nd	nd	1.01	0.71, 1.44	0.91	C
				Quartile 2	nd	nd	1.26	0.89, 1.80		
				Quartile 3	nd	nd	1.00	0.71, 1.41		
				Quartile 4	nd	nd	**1**	**Reference**		
Gann 1996[66] PHS [8850273]	19-50 51-70	Prostate cancer (232; 414)	6 (mean)	15.7-53.3	nd	nd	1.00	nd	0.82	C
				53.4-70.9	nd	nd	1.10	nd		
				71-93.5	nd	nd	1.16	nd		
				93.6-194	nd	nd	0.92	0.56, 1.50		
		Prostate cancer; age ≤61 y		15.7-53.3	nd	nd	1.00	nd	nd	
				53.4-70.9	nd	nd	1.19	nd		
				71-93.5	nd	nd	1.75	nd		
				93.6-194	nd	nd	1.48	0.73, 2.98		
		Prostate cancer; age >61 y		15.7-53.3	nd	nd	1.00	nd	nd	
				53.4-70.9	nd	nd	1.00	nd		
				71-93.5	nd	nd	0.82	nd		
				93.6-194	nd	nd	0.76	0.39, 1.47		

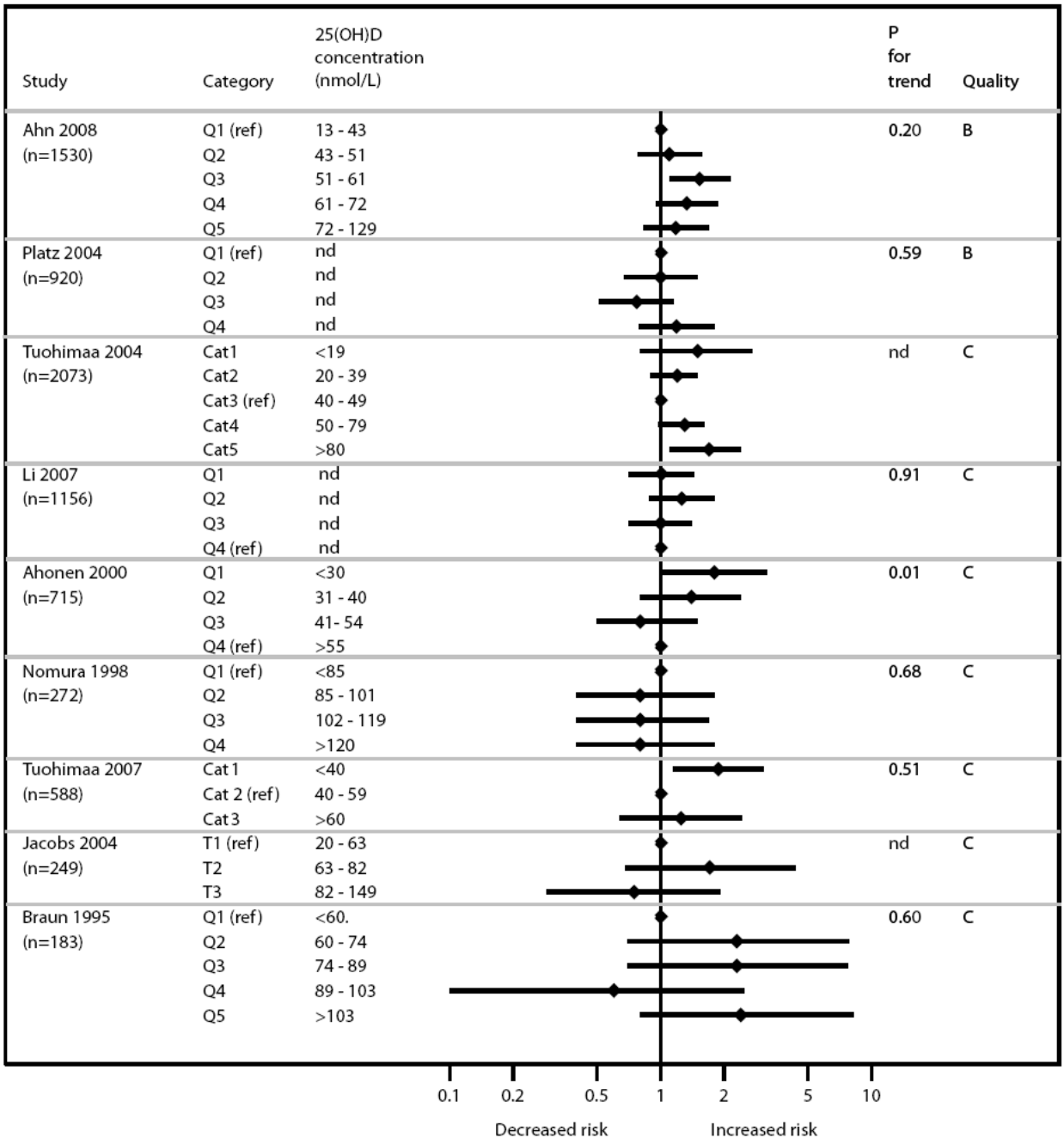
continued

Author Year Study Name PMID	Life Stage (male), y	Outcome (no. of cases; no. of control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of cases	No. of control	Adjusted OR	95% CI	P for trend	Study Quality
Corder 1993[58] [8220092]	19-50 51-70	Prostate cancer (181; 181)	>5 (mode)	60.0 (case) vs. 50.5 (control) (est.)	181	181	-	-	-	C
		Mortality prostate cancer		nd	51	nd	-	-	-	
Ahonen 2000[55] Helsinki Heart [11075874]	19-50 51-70	Prostate cancer (149; 566)	8-14 (mode)	< 30[C]	48	131	1.8	1.0, 3.2*	0.01	C
				31-40	41	143	1.4	0.8, 2.4		
				41-54	26	148	0.8	0.5, 1.5		
				> 55	34	144	**1**	**Reference**		
		Prostate cancer in those <52 years old at entry		≤40	nd	nd	3.5	1.7, 7.0*		
				>40	nd	nd	1			
		Prostate cancer in those >51 years old at entry		≤40	nd	nd	1.2	0.7, 2.1		
				>40	nd	nd	1			
Nomura 1998[62] Honolulu Heart [9794175]	19-50 51-70	Prostate cancer (136; 136)	16 (mean)	<85[D]	38	34	**1**	**Reference**	0.68	C
				85-101	35	36	0.8	0.4, 1.8		
				102-119	30	32	0.8	0.4, 1.7		
				≥120	33	34	0.8	0.4, 1.8		
Tuohimaa 2007[65] Helsinki Heart [17301263]	19-50 51-70	Prostate cancer (132; 456)	10.8 (mean)	<40	-	-	1.88	1.15, 3.08*		C
				40-59	-	-	**1**	**Reference**		
				≥60	-	-	1.25	0.64, 2.43		
Jacobs 2004[59] NPC [15225833]	51-70	Prostate cancer (83; 166)	5.1 (mean)	20-63.3	26	58	**1**	**Reference**	0.51	C
				63.4-81.9	33	49	1.71	0.68, 4.34		
				82-149	24	59	0.75	0.29, 1.91		
Braun 1995[57] WCC [7612803]	19-50 51-70	Prostate cancer (61; 122)	14 (mean)	<60.1	7	24	**1**	**Reference**	0.60	C
				60.1-73.8	17	25	2.3	0.7, 7.8		
				73.9-88.5	16	24	2.3	0.7, 7.7		
				88.6-103	4	25	0.6	0.1, 2.5		
				>103	17	24	2.4[E]	0.8, 8.2		
Baron 2005[56] CPP [15767334][F]	19-50 51-70	Prostate cancer (70 cases in a total of 672)[F]	<4 (34%)	<62.9	nd	NA	**1**	**Reference**	0.70	C
				62.9-84.9	nd	NA	1.22	0.66, 2.26		
				85	nd	NA	0.32	0.72, 2.43		

*Statistically significant (P<0.05)

[A] Cut points separated by analytical run; season, distributions among control (see Table 3 in original study)
[B] Cut points based on control standardized by season of collection
[C] Cut points based on total original cohort
[D] Cut points based on control frequency
[E] Unadjusted
[F] This is a cohort study, not a nested case-control study

Figure 7. Prostate cancer risk stratified by vitamin D concentration



Colorectal cancer.

Synopsis.

No qualified systematic reviews have evaluated the association between 25(OH)D concentrations and colorectal cancer mortality or incidence. One B quality RCT of elderly population reported no significant difference in colorectal cancer mortality or incidence between supplemental vitamin D_3 and no supplements. One B quality cohort study found an inverse association between higher 25(OH)D concentrations and the risk of colorectal cancer mortality (HR 0.28, highest compared to lowest tertile). Two B quality nested case-control studies of women found a trend between higher 25(OH)D serum concentrations and lower risk of colorectal cancer incidence (trend analysis). Another two B quality nested case-control studies of men, and one B quality and two C quality nested case-control studies of both sexes reported no significant association between 25(OH)D concentrations and risk of colorectal cancer or colon cancer.

Detailed presentation of supplemental vitamin D and colorectal caner (Tables 20 & 21).

An RCT compared supplemental vitamin D_3 (100,000 IU every 4 months) with placebo in 2686 elderly participants with a mean age of 75 years in the United Kingdom (latitude 52° N). [44] Colorectal cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin D_3 supplementation had no significant effect on the prevention of colorectal cancer mortality (P=0.33) or incidence (P=0.94). This trial was rated B because it did not report in sufficient detail the randomization method, and the outcome ascertainment was based on death certificates or self-reported data, not verified with another objective documents (e.g., medical records or pathology reports).

Findings per age and sex.

The same British trial reported no significant difference in colorectal cancer mortality or incidence between the vitamin D supplements group and the placebo at 5 years in men (P=0.96 and 0.59, respectively). In women, the trial also found no significant difference in colorectal cancer incidence between the two groups (P=0.32), whereas the risk of colorectal cancer mortality in the supplements group was significantly decreased compared to the placebo (0/326 deaths vs. 4/323 deaths; HR, not reported; P=0.04).

Findings per special populations.

No subgroup data were available regarding special populations (e.g., obese participants, smokers, ethnic groups, or users of contraceptives).

Table 20. Vitamin D and colorectal cancer: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 2003[44] Oxford, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65-85) 76%	25(OH)D: 53.4 nmol/L Calcium intake= 742 mg/day (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs placebo every 4 months	Participants taking ≥80% of study medication: 76%[A]	Previous CVD: 28%, previous cancer: 6%, steroids user: 5%, and HRT taker: 7%

CVD = cardiovascular disease; HRT = hormone replacement therapy.

[A] No difference between the vitamin D and the placebo arm.

Table 21. Vitamin D and colorectal cancer: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex (Subgp)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 2003[44] [12609940]	65-85 y, Both sexes	CRC, mortality	2°	5 y	Vit D_3 100,000 IU every 4 mo	7	1345	Age adj HR (Vit D/Placebo)	0.62	0.24, 1.60	0.33	B
					Placebo	11	1341					
		CRC, incidence	2°		Vit D_3	28	1345	Age adj HR (Vit D/Placebo)	1.02	0.60, 1.74	0.94	
					Placebo	27	1341					
	65-85 y, Men	CRC, mortality	2°	5 y	Vit D_3	7	1019	Age adj HR (Vit D/Placebo)	0.97	0.34, 2.78	0.96	
					Placebo	7	1018					
		CRC, incidence	2°		Vit D_3	25	1019	Age adj HR (Vit D/Placebo)	1.18	0.65, 2.12	0.59	
					Placebo	21	1018					
	65-85 y, Women	CRC, mortality	2°	5 y	Vit D_3	0	326	Age adj HR (Vit D/Placebo)	NA	NA	0.04	
					Placebo	4	323					
		CRC, incidence	2°		Vit D_3	3	326	Age adj HR (Vit D/Placebo)	0.49	0.12, 1.98	0.32	
					Placebo	6	323					

Detailed presentation of 25(OH)D concentrations and colorectal cancer (Tables 22 & 23; Figures 8, 9, & 10).

A total of seven nested case-control studies evaluated the associations between 25(OH)D concentrations and risk of colorectal cancer[67-71] or colon cancer.[72,73] The number of pairs of cases and controls in these studies ranged from 101 to 588. Another cohort study comprising 16,818 adult community volunteers from the NHANES III[53] assessed the association between 25(OH)D concentrations and colorectal cancer mortality. The mean age of the subjects ranged from 44 to 66 years. Locations of the studies ranged from 20° N to 60° N. Baseline 25(OH)D concentrations ranged from 10 nmol/L to 227.5 nmol/L. No studies reported followup 25(OH)D concentrations. Time between blood drawn and the diagnosis of colorectal cancer incidence or mortality ranged from less than 1 year to 17 years. None of the studies reported power calculations. Methodological quality of five nested case-control studies[67-71] were rated B and two were rated C.[72,73] Common reasons for downgrading the quality ratings included exclusion of participants without available blood samples, no verification of cancer diagnosis, and lack of adequate statistical adjustments. The cohort study[53] was rated B because it was unclear whether cases were verified and there was no statistical adjustment for family history.

Findings per age and sex.

The NHANES III[53] analyzed data for both sexes combined. An adjusted analysis found an inverse association between 25(OH)D concentrations and the risk of colorectal cancer mortality (HR: 0.28, highest [≥80 nmol/L] compared to lowest tertile [<50 nmol/L]; P for trend = 0.02). Two studies from WCC reported colon cancer incidence for both sexes combined.[72,73] One study reported a significantly lower 25(OH)D concentrations in colon cancer cases than controls (58.9 nmol/L vs. 86.6 nmol/L; P<0.001).[73] Both studies reported no significant association between 25(OH)D concentrations and colon cancer risk by trend analysis.

Three studies, from the Japan PHC, HPFS, and ATBC respectively, provided data on adult men.[67-69] None of the studies found an association between 25(OH)D concentrations and colorectal cancer risk. Although all three studies provided data on colon cancer and rectal cancer as subgroup analysis, only HPFS reported a significant trend between higher 25(OH)D concentrations and lower risk of colon cancer (OR 0.46, highest [median 97.0 nmol/L] compared to lowest quartile [median 48.3 nmol/L]; P for trend = 0.005).[69] The HPFS also reported a subgroup analysis on men aged 65 years or older.[69] No significant association was reported between 25(OH)D concentrations and colorectal cancer risk by trend analysis.

The Japan PHC and HPFS compared 25(OH)D concentrations between colorectal cancer cases and controls.[68,69] Neither reported a significant difference. One study explored subgroup analyses. Only the rectal cancer cases had significantly lower 25(OH)D concentrations compared to the controls (55 nmol/L for cases vs. 110 nmol/L for controls; P = 0.005).[68]

Two nested case-control studies from the NHS and Japan PHC provided data on adult women.[68,70] The NHS reported a trend between higher 25(OH)D concentrations and lower colorectal cancer risk (OR 0.53, highest [median 99.1 nmol/L] compared to lowest quintile [median 40.2 nmol/L]; P for trend = 0.02).[70] This trend remained significant in a subgroup analysis of women age 60 years or older (OR 0.35 between the highest quintiles [median 99.1 nmol/L] and lowest [median 40.2 nmol/L]; P for trend = 0.006) or in rectal cancer alone (OR 0.31, highest [median 92.4 nmol/L] compared to lowest tertile [median 44.4 nmol/L]; P for trend = 0.03).[70] The WHI focused on postmenopausal women.[71] A significant trend was reported

between higher 25(OH)D concentrations and lower colorectal cancer risk (OR 2.53, between highest [≥58.4 nmol/L] and lowest quintiles [<31.0 nmol/L]; P for Trend = 0.02).

The Japan PHC compared 25(OH)D concentrations between cases and controls; no significant difference was reported.[68]

Findings per special populations.

No subgroup data were available regarding the association between 25(OH)D concentrations and colorectal cancer risk in obese persons. One study exclusively included male smokers aged between 50 and 69 years,[67] and reported no significant association between 25(OH)D concentrations and colorectal cancer risk by trend analysis. Another study that exclusively included white population also found no association.[72] In addition, another study that focused on women who were taking hormone replacement therapy reported no significant association between 25(OH)D and colorectal cancer.[70]

Findings excluding early cases.

Three studies performed sensitivity analyses on the association between 25(OH)D concentrations and colorectal cancer risk by excluding cases diagnosed within the first 1 to 2 years after blood draw.[67,69,70] One study found a significant association between higher 25(OH)D concentrations and lower colon cancer risk (OR 0.3, between highest [>48.2 nmol/L] and lowest quartiles [≤ 24.5 nmol/L]; P for Trend = 0.04), which was not significant in main analysis.[67] Otherwise, the results were not materially different from the main analysis.

Findings on 1,25-Dihydroxyvitamin D.

A total of three studies evaluated the associations between $1,25(OH)_2D$ concentrations and colorectal cancer risk [67,70] or colon cancer.[73] None of the studies found a significant association by trend analysis. One study reported no significant association between $1,25(OH)_2D$ concentrations and rectal cancer risk.[67]

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The analysis of the NHANES III with a mean age of 44 years included participants mostly within this life stage. The study found an inverse association between 25(OH)D and colorectal cancer mortality.
- **51 – 70 y** The seven nested case-control studies included people with a mean age ranged from 55 to 66 years. A trend between higher 25(OH)D concentrations and lower colorectal cancer risk was found in two studies of women. Out of five studies that separately assessed the risk of colon cancer and rectal cancer, only one study of men and another study of women found trends between higher 25(OH)D concentrations and lower risks of colon cancer and rectal cancer, respectively. Otherwise, no association was found between 25(OH)D concentrations and cancer risk.
- **≥71 y** One RCT with a mean age of 75 included participants mostly within this life stage. The trial found no difference in colorectal cancer mortality or incidence between supplemental vitamin D and no supplements.

- **Postmenopause** One study and a subgroup analysis in another study focused on postmenopausal women. A trend between higher 25(OH)D concentrations and lower colorectal cancer risk was found in these two studies.
- **Pregnant & lactating women** Not reviewed

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies[A]

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Freedman 2007[53] NHANES III US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Any 44 (≥17) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Colorectal cancer mortality stratified by prespecified baseline 25(OH)D cut points	X	X	X	X	X	X	White: 71%; Black: 14%; Hispanic: 6%; Others: 9%
Nested case-control												
Braun 1995[73] WCC Maryland, US (38°N) [329893]	• Health status • Mean age (range), y • Male (%)	Any 55 (nd) Nd	• Assay method • Season blood drawn	RIA (Horris 1993) Fall	• 25(OH)D levels between cases and controls • Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		
Feskanich 2004[70] NHS US (various) [15342452]	• Health status • Mean age (range), y • Male (%)	Any 60 (43-70) 0	• Assay method • Season blood drawn	RIA (Horris 1997) All	Colorectal cancer risk stratified by baseline 25(OH)D quintiles	X	X	X	X	X	X	Aspirin user (>10 y): 10%; Hormone replacement therapy: 34%
Garland 1989[72] WCC Maryland, US (38°N) [2572900]	• Health status • Mean age (range), y • Male (%)	Any 63 (nd) 50	• Assay method • Season blood drawn	HPLA (Clemens 1982) Fall	• 25(OH)D levels between cases and controls • Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		White: 100%
Otani 2007[68] Japan PHC Japan (various) [17622244]	• Health status • Mean age (range), y • Male (%)	Any Men: 57 (40-69); Women: 56 (40-69)	• Assay method • Season blood drawn	CPBA (Haddad 1971) All	• 25(OH)D levels between cases and controls • Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	

continued

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Tangrea 1997[67] ATBC Finland (~60°N) [9242478]	• Health status • Mean age (range), y • Male (%)	Smoker[B] 60 (50-69) 100	• Assay method • Season blood drawn	RIA (Horris 1993) All	Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X		X	X	
Wactawski-Wende 2006[71] WHI US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Post-menopausal women[C] Nd (50-79) 0	• Assay method • Season blood drawn	RIA (DiaSorin) All	Colorectal cancer risk stratified by baseline 25(OH)D quartiles		X	X	X		X	White: 83%; Black: 9%; Hispanic: 4% Others: 4%
Wu 2007[69] HPFS US (various) [17623801]	• Health status • Mean age (range), y • Male (%)	Smoker 5% 66 (nd) 100	• Assay method • Season blood drawn	RIA (Horris 1997) All	• 25(OH)D levels between cases and controls • Colorectal cancer risk stratified by baseline 25(OH)D quintiles	X	X	X	X	X	X	Aspirin user in 1994: 40%; Current smoker: 5%

[A] This table is ordered alphabetically by study author.
[B] Participants of a lung cancer prevention 2 by 2 RCT of alpha-tocopherol and beta-carotene.
[C] Participants of a hip fracture prevention RCT of vitamin D3 and calcium

Table 23. Vitamin D and colorectal cancer: Results of observational studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Cohort study										
Colorectal cancer mortality										
Women										
Freedman 2007[53] [17971526]	19-50[A] 51-70 ≥71	Colorectal Cancer Mortality (66/16818; 0.004)	nd	<50	28	~5606	**1**	**Reference**	0.02	B
				50-80	24	~5606	0.44	0.20, 0.95*		
				≥80	14	~5606	0.28	0.11, 0.68*		
Nested case-control study										
Colorectal cancer										
Men										
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Colorectal cancer (N=196 cases; 392 controls)	1-13	<57.2	43	74	**1**	**Reference**	0.39	B
				57.2-69.0	40	85	0.76	0.42, 1.4		
				69.0-80.2	36	85	0.76	0.39, 1.5		
				≥80.2	44	80	0.73	0.35, 1.5		
Wu 2007[69] HPFS [17623801]	19-50 51-70[A] ≥71	Colorectal cancer (179 cases; 356 controls)	1-9	46, median	45	71	**1**	**Reference**	0.24[B]	B
				62.5	44	71	0.97	0.55, 1.70		
				72.8	30	68	0.66	0.35, 1.24		
				83.3	23	74	0.51	0.27, 0.97*		
				98.5	37	72	0.83	0.45, 1.52		
	19-50 51-70[A]	Colorectal cancer, age <65		48.2, median	25	34	**1**	**Reference**	0.13	
				66.8	15	28	1.03	0.36, 2.91		
				80.0	9	30	0.38	0.12, 1.26		
				97.0	14	36	0.45	0.15, 1.40		
	51-70[A] ≥71	Colorectal cancer, age ≥65		48.2, median	34	55	**1**	**Reference**	0.34	
				66.8	36	61	0.97	0.50, 1.87		
				80.0	19	58	0.56	0.27, 1.15		
				97.0	27	54	0.83	0.39, 1.75		
Tangrea 1997[67] ATBC [9242478]	19-50 51-70[A]	Colorectal cancer (146 cases; 292 controls)	1-8	≤24.5	46	72	**1**	**Reference**	0.13	B
				24.5-34.7	35	73	0.7	0.4, 1.3		
				34.7-48.2	36	73	0.8	0.4, 1.3		
				>48.2	29	72	0.6	0.3, 1.1		

continued

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Women										
Wactawski-Wende 2006[71] WHI [16481636]	Post-menopausal women	Colorectal cancer (306 cases; 306 controls)	1-12	<31.0	88	67	2.53	1.49, 4.32	0.02	B
				31.0-42.3	80	73	1.96	1.18, 3.24*		
				42.4-58.3	78	73	1.95	1.18, 3.24*		
				≥58.4	60	93	**1**	**Reference**		
Feskanich 2004[70] NHS [15342452]	19-50 51-70[A]	Colorectal cancer (192 cases; 384 controls)	1-11	40.2, median	53	77	**1**	**Reference**	0.02[C]	B
				55.1	47	79	0.93	0.53, 1.63		
				66.7	35	75	0.79	0.44, 1.40		
				77.5	29	77	0.58	0.31, 1.07		
				99.1	29	75	0.53	0.27, 1.04		
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Colorectal cancer (179 cases; 358 controls)	1-13	<57.2	41	77	**1**	**Reference**	0.74	B
				57.2-69.0	34	73	1.0	0.55, 1.9		
				69.0-80.2	44	71	1.2	0.65, 2.3		
				≥80.2	41	76	1.1	0.50, 2.3		
Colon cancer										
Both sexes										
Braun 1995[73] WCC [329893]	19-50 51-70[A] ≥71	Colon cancer (57 cases; 114 controls)	1-17	<43	nd	nd	**1**	**Reference**	0.57	C
				43.0-51.5	nd	nd	0.3	0.1, 1.0		
				51.5-61.8	nd	nd	0.5	0.2, 1.5		
				61.8-75.3	nd	nd	0.7	0.2, 2.0		
				≥75.3	nd	nd	0.4	0.1, 1.4		
Garland 1989[72] WCC [2572900]	19-50 51-70[A] ≥71	Colon cancer (34 cases; 67 controls)	1-9	10 to <50	9	8	**1**	**Reference**	0.41	C
				50.0-67.5	7	13	0.48	0.13, 1.80		
				67.5-82.5	5	18	0.25	0.06, 0.98*		
				82.5-105	4	17	0.21	0.05, 0.89*		
				105-227.5	9	11	0.73	0.20, 2.66		
Men										
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Colon cancer (141 cases; 282 controls)	1-13	<57.2	25	54	**1**	**Reference**	0.70	B
				57.2-69.0	27	55	0.98	0.48, 2.0		
				69.0-80.2	29	66	1.0	0.48, 2.3		
				≥80.2	38	62	1.2	0.51, 2.7		

continued

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Wu 2007[69] HPFS [17623801]	19-50 51-70[A] ≥71	Colon cancer (139 cases; 276 controls)	1-9	48.3, median	49	66	**1**	**Reference**	0.005[D]	B
				66.8	44	68	0.74	0.42, 1.33		
				80.0	17	68	0.29	0.14, 0.59*		
				97.0	29	74	0.46	0.24, 0.89*		
Tangrea 1997[67] ATBC [9242478]	19-50 51-70[A]	Colon cancer (91 cases; 182 controls)	1-8	≤24.5	30	47	**1**	**Reference**	0.69[E]	B
				24.5-34.7	18	47	0.6	0.3, 1.2		
				34.7-48.2	22	45	0.8	0.4, 1.6		
				>48.2	21	42	0.8	0.4, 1.6		
Women										
Feskanich 2004[70] NHS [15342452]	19-50 51-70[A]	Colon cancer (148 cases; 296 controls)	1-11	41.2, median	41.2	75	**1**	**Reference**	0.17	B
				59.7	59.7	71	1.03	0.56, 1.89		
				73.3	73.3	77	0.54	0.28, 1.03		
				98.1	98.1	72	0.70	0.35, 1.38		
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Colon cancer (115 cases; 230 controls)	1-13	<57.2	21	53	**1**	**Reference**	0.12	B
				57.2-69.0	27	48	1.7	0.78, 3.6		
				69.0-80.2	27	41	2.1	0.90, 4.7		
				≥80.2	31	53	2.1	0.78, 5.6		
Rectal cancer										
Men										
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Rectal cancer (55 cases; 110 controls)	1-13	<57.2	18	20	**1**	**Reference**	0.06	B
				57.2-69.0	13	30	0.17	0.02, 1.2		
				69.0-80.2	7	19	0.25	0.05, 1.3		
				≥80.2	6	18	0.075	0.005, 0.99		
Tangrea 1997[67] ATBC [9242478]	19-50 51-70[A]	Rectal cancer (55 cases; 110 controls)	1-8	≤24.5	16	25	**1**	**Reference**	0.06[F]	B
				24.5-34.7	17	26	0.9	0.4, 2.4		
				34.7-48.2	14	28	0.8	0.3, 2.0		
				>48.2	8	30	0.4	0.1, 1.1		

continued

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Wu 2007[69] HPFS [17623801]	19-50 51-70[A] ≥71	Rectal cancer (40 cases; 80 controls)	1-9	53.0, median	11	30	**1**	**Reference**	0.08	B
				73.3	15	28	1.74	0.61, 5.00		
				93.5	14	22	3.32	0.87, 12.69		
Women										
Otani 2007[68] Japan PHC [17622244]	19-50 51-70[A]	Rectal cancer (64 cases; 128 controls)	1-13	<57.2	20	24	**1**	**Reference**	0.17	B
				57.2-69.0	7	25	0.26	0.07, 1.0		
				69.0-80.2	17	30	0.46	0.15, 14		
				≥80.2	10	23	0.33	0.08, 1.3		
Feskanich 2004[70] NHS [15342452]	19-50 51-70[A]	Rectal cancer (44 cases; 88 controls)	1-11	44.4, median	24	31	**1**	**Reference**	0.03	B
				66.2	10	26	0.52	0.14, 1.93		
				92.4	10	31	0.31	0.08, 1.31		

* Statistically significant (P<0.05)

[A] Most representative life stage.
[B] P for trend = 0.31 when cases diagnosed within 2 years of blood collection were excluded.
[C] Results were not notably changed when cases diagnosed within the first year after blood collection were excluded (P for trend not reported). Subgroup analyses per age were also reported as follows: Age ≥ 60, OR = 0.35 (95% CI 0.14, 0.87) between the lowest and highest quintiles; P for trend = 0.006. Age < 60, OR = 1.36 (95% CI 0.48, 3.92) between the lowest and highest quintiles; P for trend = 0.70.
[D] P for trend = 0.008 when cases diagnosed within 2 years of blood collection were excluded.
[E] P for trend = 0.58 when cases diagnosed within 2 years of blood collection were excluded.
[F] P for trend = 0.04 when cases diagnosed within 2 years of blood collection were excluded.

Figure 8. Colorectal cancer risk stratified by vitamin D concentration

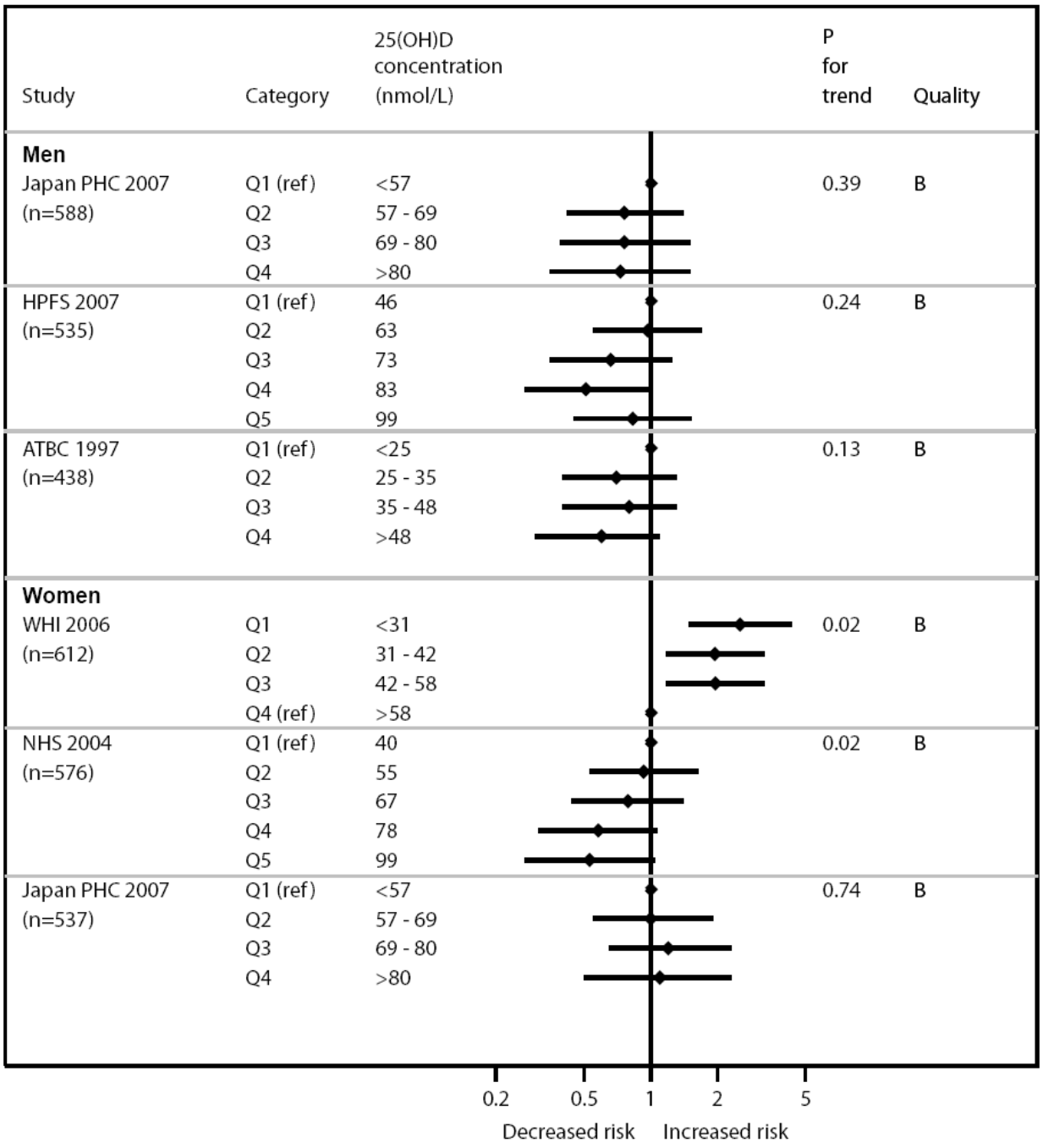


Figure 9. Colon cancer risk stratified by vitamin D concentration

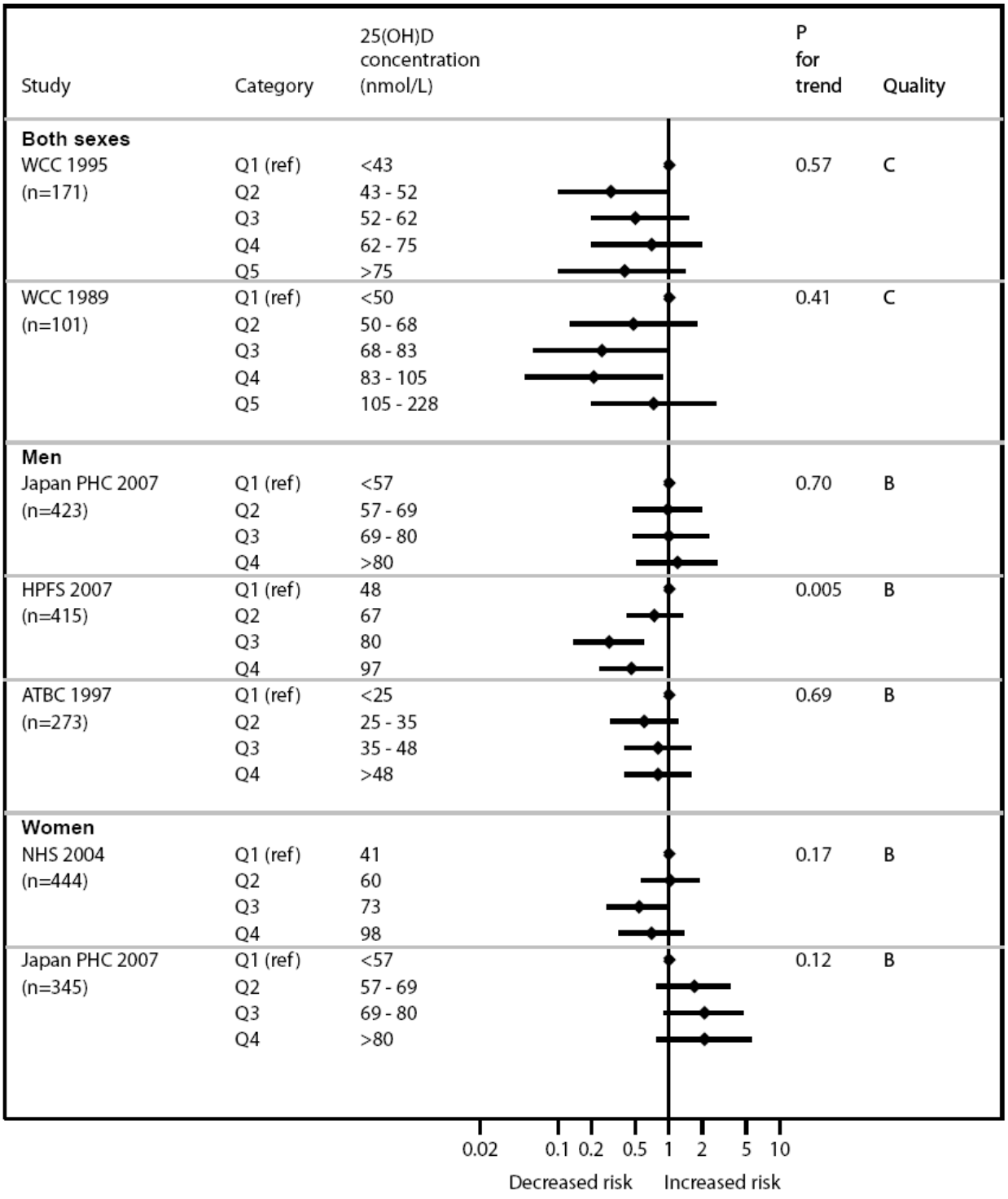
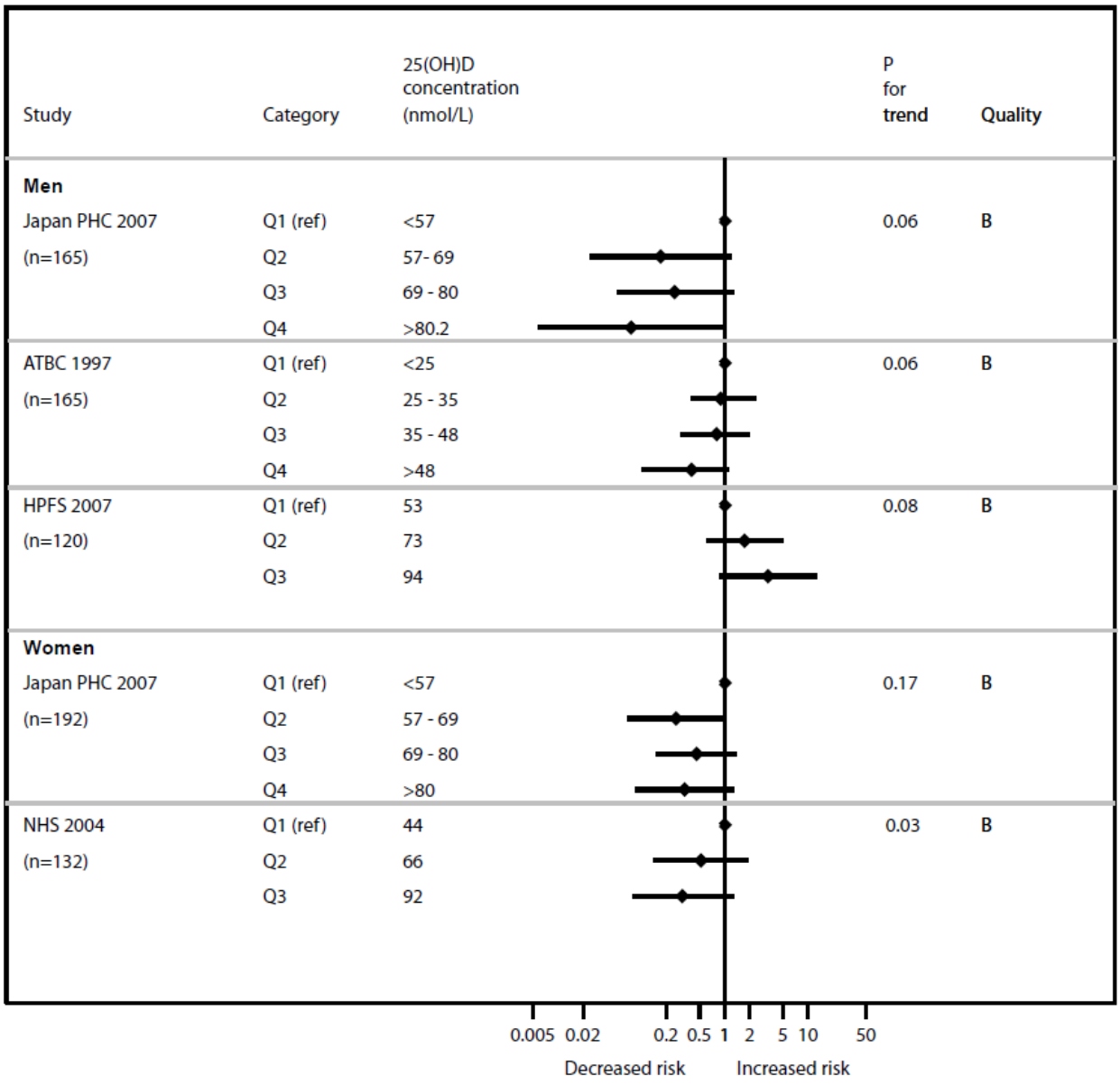


Figure 10. Rectal cancer risk stratified by vitamin D concentration



Colorectal adenoma.

Synopsis.

No systematic reviews have evaluated the association between 25(OH)D concentrations and the risk of colorectal adenoma. One B quality nested case-control study in women found no significant association between 25(OH)D concentrations and the risk of colorectal adenoma.

Detailed presentation (Tables 24 & 25).

One nested case-control study within the NHS evaluated the relationship between 25(OH)D concentrations and the risk of colorectal adenoma in women.[74] At 5 years, an adjusted analysis found no significant association between 25(OH)D concentrations and the incidence of colorectal adenoma by trend analysis. Subgroup analyses also found no significant association between 25(OH)D concentrations and the incidence of colon or rectal adenoma. No subgroup data were available regarding age or other special populations (e.g., obese, smokers, ethnic groups, or users of contraceptives). This study was rated B because it excluded more than 50 percent of participants of the original cohort because their blood samples were not available.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** A proportion of participants in the NHS was in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **51 – 70 y** The analysis of the NHS included female participants mostly within this life stage. The study found no association between 25(OH)D and the incidence of colorectal adenoma.
- **≥71 y** A proportion of participants in the NHS was in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Postmenopause** The analysis of NHS partially included postmenopausal women. However, no unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Pregnant & lactating women** Not reviewed

Table 24. Vitamin D and colorectal adenoma: Characteristics of observational studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Nested case-control												
Platz 2000[74] NHS US (various) [11045788]	• Health status • Mean age (SD), y • Male (%)	Any 59 (7) 0	• Assay method • Season blood drawn	RIA (Horris 1993) All	• Colorectal adenoma risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	Aspirin user: 26%; Hormone replacement therapy: 36%

Table 25. Vitamin D and colorectal adenoma: Results of observational studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Nested case-control study										
Colorectal adenoma										
Women										
Platz 2000[74] NHS [11045788]	19-50 51-70[A] ≥71	Colorectal adenoma (326 cases; 326 controls)	5	16.3, median	103	82	**1**	**Reference**	1.0	B
				22.6	62	80	0.64	0.41, 1.00		
				28.3	61	82	0.58	0.36, 0.95		
				38.0	100	82	1.04	0.66, 1.66		
Colon adenoma										
Women										
Platz 2000[74] NHS [11045788]	19-50 51-70[A] ≥71	Colon adenoma (261 cases; 261 controls)	5	16.3, median	79	64	**1**	**Reference**	1.0	B
				22.6	55	64	0.71	0.43, 1.18		
				28.3	51	69	0.60	0.35, 1.02		
				38.0	76	64	1.02	0.60, 1.73		
Rectal adenoma										
Women										
Platz 2000[74] NHS [11045788]	19-50 51-70[A] ≥71	Rectal adenoma (65 cases; 65 controls)	5	16.3, median	24	18	**1**	**Reference**	0.9	B
				22.6	7	16	0.38	0.12, 0.19		
				28.3	10	13	0.34	0.08, 1.42		
				38.0	24	18	1.59	0.50, 5.03		

* Statistically significant (P<0.05)

[A] Most representative life stage

Breast cancer.

Synopsis.

No qualified systematic reviews evaluated the association between vitamin D and calcium intake or serum 25(OH)D concentration and risk of breast cancer. One cohort study compared serum 25(OH)D concentrations and the risk of breast cancer-specific mortality,[53] and two nested case-control studies compared 25(OH)D concentrations and the risk of breast cancer.[75,76] The cohort study utilizing NHANES III data found significant decrease in breast cancer-specific mortality during 9 years of followup in those with serum concentration of 25(OH)D greater than 62 nmol/L. The Nurses' Health Study and Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, however, found no significant relationship between serum concentration of 25(OH) D and risk of breast cancer diagnosis in either pre- or postmenopausal women during 7 to 12 years of followup.[75,76] All three studies were rated B quality.

Detailed presentation (Tables 26 & 27).

The NHANES III study followed 16,818 adults with a mean age of 44 years with a background calcium intake on average of about 812 mg/day (from diet and supplements). [53] The study included 71 percent non-Hispanic white, 14 percent non-Hispanic black, 6 percent Mexican American, and 9 percent from other races. During 9 years of followup, women with serum concentration of 25(OH) D greater than 62 nmol/L had a hazard ratio of 0.28 for breast cancer-specific mortality compared to those with 62 nmol/L or lower (95 percent CI 0.08-0.93). The breast cancer-specific mortality was one of many cancer-specific mortality outcomes reported in this study.

Two nested case-control studies of women with a mean age of 57 years and 67 years, respectively, found no relationship between serum 25(OH)D concentrations and risk of breast cancer.[75,76] However, in the second study, when compared with the lowest quintile, quintiles 3 to 5 were associated with nonsignificantly elevated risks. In multivariable adjusted analyses, the risk associated with 25(OH)D levels below 15 ng/mL compared with higher levels was 0.81 (95 percent CI 0.59, 1.12).[76]

Findings by age and sex.

In the one nested case-control study (methodological quality B) including both premenopausal and postmenopausal women, no relationship was found between vitamin D levels and risk of breast cancer. However, in this study, there was a statistically significant trend towards decreased risk of breast cancer among women older than 60 years of age with serum concentration of 25(OH)D greater than 62 nmol/L.

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** A followup study of NHANES III including women with a mean age of 44 years found a decreased mortality (hazard ratio 0.28) due to breast cancer among those with serum concentration of 25(OH)D greater than 62 nmol/L.

- **51 – 70 y** Two nested case-control studies of women with a mean age of 57 years and 67 years, respectively, found no relationship between vitamin D levels and risk of breast cancer. However, in one of these studies, there was a statistically significant trend towards decreased risk of breast cancer among women older than 60 years of age with serum concentration of 25(OH)D greater than 62 nmol/L.
- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** Not reviewed

Table 26. Vitamin D and breast cancer: Characteristics of observational studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Freedman 2007[53] NHANES III US (38º N) [17971526]	• Health status • Mean age (range/SD), y	Non-institutionalized 44 (ND)	• Assay method • Season blood drawn	RIA All year	Breast cancer risks: Quintile 1 vs. Quintile 2	X	X	X		X	X	
Nested Case-Control												
Bertone-Johnson 2005[75] NHS US (38º N) [16103450]	• Health status • Mean age (range/SD), y	No Cancer 57 (7.0)	• Assay method • Season blood drawn	RIA All year	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5	X	X	X	X		X	
Freedman 2008[76] PLCO Trial US (38º N) [18381472]	• Health status • Mean age (range/SD), y	No Cancer 67 (ND)	• Assay method • Season blood drawn	RIA Dec-Sep	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5	X	X	X	X		X	

Table 27. Vitamin D and breast cancer: Results of observational studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Cohort											
Freedman 2007[53] NHANES III [17971526]	All Adults	Breast cancer mortality (28/ND)[A]	105 mo	25(OH)D	<63	20	ND	**1**	**Reference**	NS	B
					≥63	8	ND	HR 0.28	0.08, 0.93*		
Nested Case-Control											
Bertone-Johnson 2005[75] NHS [16103450]	Pre- and Post-menopausal	Breast cancer (701/1425)	<1-82 mo	25(OH)D	≤50 (1st batch) ≤70 (2nd batch) ≤45 (3rd batch)	159	297	**1**	**Reference**	nd	B
					51 - 70 72 - 85 47 to 60	149	278	0.95	0.66, 1.36		
					72 - 82 87 - 97 62 - 72	125	266	0.74	0.51, 1.06		
					85 - 97 100 - 117 75 - 90	144	296	0.80	0.58, 1.11		
					≥100 ≥120 ≥92	124	265	0.73	0.49, 1.07		
		Breast cancer <60 y (701/1425)				97	191	**1**	**Reference**	NS	
						84	170	0.96	0.62, 1.49		
						77	164	0.80	0.51, 1.26		
						90	192	0.85	0.55, 1.32		
						70	146	0.92	0.57, 1.48		
		Breast cancer ≥60 y (701/1425)				62	109	**1**	**Reference**	**0.03**	
						65	114	1.07	0.60, 1.92		
						48	105	0.64	0.35, 1.16		
						54	99	0.68	0.38, 1.24		
						54	125	0.57	0.31, 1.04		

continued

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Freedman 2008[76] PLCO Cancer Screening Trial [18381472]	Pre- and Post-menopausal	Breast cancer (1005/2010)	12 y	25(OH)D	<46	172	2010	**1**	**Reference**	NS	B
					46-58	188	2010	1.02	0.75, 1.41		
					59-71	244	2010	1.36	0.99, 1.87		
					72-83	205	2010	1.13	0.82, 1.55		
					≥84	196	2010	1.04	0.75, 1.45		

* Statistically significant (P<0.05)
[A] Total number of women not reported

Pancreatic cancer.

Synopsis.

No qualified systematic reviews evaluated associations between serum vitamin D concentrations and the incidence of pancreatic cancer. Two nested case-control studies, rated A in methodological quality, evaluated the association between serum 25(OH) concentration and the risk of developing pancreatic cancer in two different populations. One study found that older adult male smokers living in Finland with higher baseline serum 25(OH)D concentration had an increased risk of exocrine pancreatic cancer compared with those with lower concentration (>65.5 vs. <32 nmol/L; OR=2.92; P for trend=0.001). The other study found that baseline 25(OH)D concentrations were not associated with the risk of overall pancreatic cancer (>82.3 vs. <45.9 nmol/L; OR=1.45; P for trend=0.49) among older adults living in the United States. However, there was an increased risk of pancreatic cancer among the study participants with higher compared to lower 25(OH)D concentrations (>78.4 vs. <49.3 nmol/L; OR=4.03) only in those living in low residential UVB exposure areas but not among those living in moderate or high residential UVB exposure areas.

Detailed presentation (Tables 28 & 29).

51 - 74 years.

One nested case-control study based on the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) in older adult male smokers aged 54 to 62 years in Finland identified 200 cases of incident exocrine pancreatic cancer.[77] These cases were matched to 400 controls. Baseline serum 25(OH)D concentration was stratified into quintiles. The odds ratio for exocrine pancreatic cancer was 2.92 (95 percent CI 1.56, 5.48) comparing 5th quintile (>65.5 nmol/L) to 1st quintile (<32 nmol/L). The result was adjusted for age, month of blood drawn, years smoked, number of cigarettes smoked per day, reporting to have quit smoking more than three consecutive visits (>1 y) during the trial (1985-1993), occupational physical activity, education, and serum retinol. The study authors excluded islet cell carcinomas from analysis because the etiology for their pathogenesis might be different from that of exocrine tumors.

Another nested case-control study based on the Prostate, Lung, Colorectal, and Ovarian Screening (PLCO) trial in older men and women aged 55 to 74 years in the United States identified 184 cases of incident pancreatic cancer.[78] These cases were matched to 368 controls. Baseline serum 25(OH)D concentration was stratified into quintiles. The odds ratio for exocrine pancreatic cancer was 1.45 (95 percent CI 0.66, 3.15) comparing 5th quintile (>82.3 nmol/L) to 1st quintile (<45.9 nmol/L). The result was adjusted for age, race, sex, date of blood draw based on 2-month blocks, BMI and smoking. The association was not significantly modified by season of blood collection (P for interaction > 0.14); but estimated residential annual solar UVB exposure significantly modified the 25(OH)D concentration and pancreatic cancer association (P for interaction = 0.015). In the joint effects models, among subjects with low estimated annual UVB residential exposure, higher compared with lower 25(OH)D concentrations were associated with increased risk of pancreatic cancer (compared with the lowest quartile, the ORs for each respective quartile were 2.52, 2.33, and 4.03; 95 percent CI 1.38, 11.79), whereas among subjects with moderate to high residential UVB exposure, 25(OH)D concentrations were not associated with pancreatic cancer. There was no significant interaction of 25(OH)D

concentration and pancreatic cancer by smoker status, sex, physical activity, or total vitamin A intake.

Findings by life stage.

- **0 – 6 mo** not reviewed
- **7 mo – 2 y** not reviewed
- **3 – 8 y** not reviewed
- **9 – 18 y** not reviewed
- **19 – 50 y** No study specifically targeted this age group.
- **51 – 70 y** One nested case-control study found that male smokers living in Finland with higher baseline serum 25(OH)D concentration had an increased risk of pancreatic cancer compared with those with lower concentration (5^{th} vs. 1^{st} quintile, >65.5 vs. <32 nmol/L: OR 2.92, 95 percent CI 1.56, 5.48, P for trend = 0.001). Another study found that baseline 25(OH)D concentrations were not associated with overall risk of pancreatic cancer among older adults living in the United States (5^{th} vs. 1^{st} quintile, >82.3 vs. <45.9 nmol/L: OR 1.45, 95 percent CI 0.66, 3.15; P for trend=0.49). However, there was an increased risk of pancreatic cancer among the study participants living in low residential UVB exposure areas (4^{th} vs. 1^{st} quartile >78.4 vs. <49.3 nmol/L: OR=4.03; 95 percent CI 1.38, 11.79).
- **≥71 y** No study specifically targeted this age group.
- **Postmenopause** not reviewed
- **Pregnant & lactating women** not reviewed

Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies

Author Year Trial/Cohort Country (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	Comments
Stolzenberg-Solomon 2006[77] ATBC Finland (60°N) [17047087]	Health status Mean age (range/SD), y Male (%)	All smokers 58 100	Assay Season blood drawn	RIA (DiaSorin) nd; but result adjusted for this variable	Exocrine pancreatic risk stratified by baseline 25(OH)D quintiles	X	X			X	X	
Stolzenberg-Solomon 2009[78] PLCO US (various) [19208842]	Health status Mean age (range), y Male (%)	DM: 10.5% 66 (55-74) 65.2	Assay Season blood drawn	RIA (Heartland Assays lab) All seasons	Pancreatic risk stratified by baseline 25(OH)D quintiles Pancreatic risk stratified by residential sun exposure levels and baseline 25(OH)D quartiles		X	X		X	X	

Table 29. Vitamin D and pancreatic cancer: Results of observational studies

Author Year Study Name PMID	Life Stage, y	Outcome (no. of cases; no. of control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of cases	No. of control	Adjusted OR	95% CI	P for trend	Study Quality
Stolzenberg-Solomon 2006[77] ATBC Finland (60°N) [17047087]	51-70, male only	Exocrine pancreatic cancer (200; 400)	11.8 (median)	<32	27	80	**1**	**Reference**	0.001	A
				32-41.1	34	80	1.30	0.70, 2.40		
				41.1-51.1	47	80	2.12	1.15, 3.90*		
				51.1-65.5	35	81	1.50	0.81, 2.76		
				>65.5	57	79	2.92	1.56, 5.48*		
Stolzenberg-Solomon 2009[78] PLCO US (various) [19208842]	51-70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y	≤45.9	44	74	**1**	**Reference**	0.49	A
				>45.9 to ≤60.3	40	74	0.97	0.47, 1.98		
				>60.3 to ≤69.5	27	73	0.86	0.40, 1.84		
				>69.5 to ≤82.3	31	74	0.84	0.39, 1.80		
				>82.3	42	73	1.45	0.66, 3.15		
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd	<49.3	22	44	**1**	**Reference**	P for interaction between low and moderate/high residential sun exposure = 0.015	
				>49.3 to <65.2	22	42	2.52	0.92, 6.90		
				>65.2 to <78.4	21	43	2.33	0.83, 6.48		
				>78.4	26	38	4.03	1.38, 11.79*		
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd	<49.3	33	48	1.97	0.80, 4.82		
				>49.3 to <65.2	15	50	0.66	0.22, 2.01		
				>65.2 to <78.4	18	49	0.91	0.31, 2.71		
				>78.4	24	54	1.45	0.53, 3.96		

* Statistically significant (P<0.05)

Vitamin D and Immunologic Outcomes

We reviewed primary studies that evaluated relationships between vitamin D and any immune function related outcomes.

Synopsis.

Analyses using NHANES III data (general adult populations living in the US) showed no significant association between baseline 25(OH)D concentrations and infectious disease mortality.

One cohort study from UK suggested a relationship between maternal 25(OH)D concentration and the risk of eczema in their children, but the analysis did not control for important potential confounders, and the 25(OH)D concentrations in children were not measured.

Detailed presentation (Tables 30 & 31).

One study analyzed NHANES III data and showed no association between baseline 25(OH)D concentrations and infectious disease.[47] NHANES III cohort represents general adult populations living in the United States. This study was rated quality C.

One cohort study from UK analyzed the serum 25(OH)D concentration in 440 white women in late pregnancy (~33 wk) and found their infants' risk of eczema at age 9 months was higher in those mothers in the top quartile of the distribution of serum 25(OH)D (>50 nmol/L) compared with those at the bottom quartile (<30 nmol/L), although the results were not statistically significant.[42] However, this analysis did not control for important potential confounders, and the 25(OH)D concentrations in children were not measured. This study was rated quality C.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** NHANES III data include people in this life stage. Analyses using NHANES III data (general adult populations living in the US) showed no significant association between baseline 25(OH)D concentrations and infectious disease mortality.
- **51 – 70 y** NHANES III data also include people in this life stage.
- **≥71 y** NHANES III data also include people in this life stage
- **Postmenopause** No data
- **Pregnant & lactating women** One cohort study from UK analyzed the serum 25(OH)D concentration in white women in late pregnancy (~33 wk) and showed a relationship between maternal 25(OH)D concentration and the risk of eczema in their children. However, this analysis did not control for important confounders, and the 25(OH)D concentrations in children were not measured.

Table 30. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Melamed 2008[47] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All	Infectious disease mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Gale 2008[42] PAHSG UK (50ºN) [17311057]	• Health status • Mean age (range/SD), y • Male (%)	singleton pregnancy <17 wk 26.3 0	• Assay method • Season blood drawn	RIA nd	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only

Table 31. Vitamin D (mother) and immunologic outcomes (offspring): Results of cohort studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Melamed 2008[47] NHANES III US (various) [18695076]	Adults, both sexes	Infectious disease mortality (N=13,331)	Median 8.7 (IRQ 7.1-10.2) y	25(OH)D	<44	nd	13331 (Total)	0.84	0.38, 1.86	nd	C
					44-60	nd	nd	0.87	0.43, 1.74		
					61-80	nd	nd	1.01	0.53, 1.93		
					>80	nd	nd	**1**	**Reference**		
Gale 2008[42] PAHSG UK (54°N) [17311057]	Pregnant women; infant at 9 mo	Atopic eczema at 9 mo (48/440; 0.11)	9 mo	Maternal 25(OH)D at late pregnancy	<30 (Quartile)	9	440 (total)	**1**	**Reference**	nd	C
					30-50	10		1.11[A]	0.43, 2.84		
					50-75	15		1.75[A]	0.73, 4.17		
					>75	14		1.62[A]	0.67, 3.89		

[A] Crude OR

Vitamin D and Pregnancy-related Outcomes

Preeclampsia.

Synopsis.

A single nested case-control study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia. The study was rated B for methodological quality.

Detailed presentation (Tables 32 & 33).

A nested case-control study evaluated the association between 25(OH)D concentration and risk of preeclampsia.[79] The study found an association between 25(OH)D concentrations less than 37.5 nmol/L (measured approximately 30 wk before outcome assessment) and increased risk of preeclampsia**.** The study was rated B for methodological quality.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** See pregnant and lactating women.
- **51 – 70 y** Not applicable
- **≥71 y** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** A single nested case-control study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia.

Other outcomes.

Synopsis.

We did not identify any eligible studies on the relationship of vitamin D with or without calcium and high blood pressure, preterm birth, or small infant for gestational age.

Table 32. Vitamin D and preeclampsia: Characteristics of nested case-control studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle
Bodnar 2007[79] PEPPS[A] US (41°N) [17535985]	• Health status • Age range, y • Male (%)	Healthy 20-29 0	• Assay method • Season blood drawn	ELISA ND	Comparison of mean 25(OH)D levels in cases and controls		x	x			

[A] Pregnancy Exposures and Preeclampsia Prevention Study

Table 33. Vitamin D and preeclampsia: Results of nested case-control studies

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Bodnar 2007[79A] PEPPS[B] US (41°N) [17535985]	Pregnancy	Preeclampsia (55/1198; 4%) [C]	ND	25(OH)D[D]	<37.5 (vs. >37.5)	49	265	5.0	1.7, 14.1	B

[A] This is a nested case-control study
[B] Pregnancy Exposures and Preeclampsia Prevention Study
[C] Incidence obtained from the "parent" cohort study in which this case control study is nested.
[D] Early in pregnancy, approximately 30 wk before outcome assessment

Vitamin D and Clinical Outcomes of Bone Health

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review (Effectiveness and Safety of Vitamin D in Relation to Bone Health) performed by the Ottawa EPC (Table 28).[6] Because the Ottawa's EPC report did not report separate analyses for the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation were presented in the "Combined Vitamin D and Calcium" section. The Ottawa EPC report also did not report separate analyses by study designs (i.e., RCTs, prospective cohorts, before and after study, and case-control studies), although the report primarily included RCTs.

The Ottawa EPC report was updated with literature published between January 2006 and September 2008, selected according to our eligibility criteria. Only RCTs qualified for inclusion.

Rickets.

Synopsis.

The Ottawa EPC report concluded that there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). According to the report, there is inconsistent evidence to determine whether there is a threshold concentration of serum 25(OH)D above which rickets do not occur.

Our updated search did not identify new RCTs examining the effect of vitamin D supplementation on rickets.

Detailed presentation (Table 34).

Ottawa EPC Report: Rickets - infants (0 through 12 months) and young children (1 through 5 years).

Overall, there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). There is inconsistent evidence to determine whether there is a threshold concentration of serum 25(OH)D above which rickets do not occur.

Six studies (one RCT, three before-after and two case-control studies) reported mean or median serum 25(OH)D concentrations < 30 nmol/L in children with rickets whereas the other studies reports the mean or median 25(OH)D concentrations were above 30 nmol/L (and up to 50 nmol/L). In seven of eight case-control studies, serum 25(OH)D concentrations were lower in the children with rickets compared with controls.

Findings by life stage.

- **0 – 6 mo** The Ottawa EPC report included infants and young children and concluded that there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). There were no new data since the Ottawa EPC report.
- **7 mo – 2 y** The Ottawa EPC report included infants and young children. There were no new data since the Ottawa EPC report.

- **3 – 8 y** The Ottawa EPC report included young children. There were no new data since the Ottawa EPC report.
- **9 – 18 y** Not reviewed
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed
- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** Not reviewed

Table 34. Summary of systematic review of the effect of vitamin D on bone health

Author Year [PMID]	Cranney 2007[6] [18088161]
Design	Systematic review of RCTs and observational studies
Population	• Include all ages • Exclude secondary causes of osteoporosis (e.g., glucocorticoid-induced, renal or liver disease) • Exclude studies on the treatment of vitamin D-dependent rickets (to minimize clinical heterogeneity as treatments is often nondietary sources of vitamin D)
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include vitamin D_2 or D_3 with or without calcium. • Exclude vitamin D preparations, calcitriol, α-calcidol (because they are not nutritional supplements, and have different safety profile) Comparator: • No vitamin D or lower doses/levels of vitamin D
Results	See text for summary results for the following outcomes in both vitamin D and combined vitamin D and calcium sections of the report: • Rickets • Fractures, falls, or performance measures • Bone mineral density or bone mineral contents • How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D Concentrations • Adverse events
Comments	Case-control studies were included but always summarized separately from cohort studies and RCTs. Meta-analyses were performed to pool results from RCTs only.

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Fractures, falls, or performance measures.

Synopsis.

Overall, the Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and the risk of fractures, falls, and performance measures among postmenopausal women or elderly men are inconsistent.[6]

Findings from three additional RCTs (published after the Ottawa EPC report)[80-82] also did not show significant effects of either vitamin D_2 or D_3 supplementation (daily doses ranged from 400 IU to 822 IU) in reducing the risk of total fractures or falls in elderly populations (≥71 years old).

Detailed presentation (Tables 35 & 36).

Ottawa EPC Report: Fractures - Postmenopausal women or elderly men.

Overall, there is inconsistent evidence for an association between serum 25(OH)D concentrations and the risk of fractures. Fifteen studies (three prospective cohorts and twelve case-controls) reported on the association between serum 25(OH)D concentrations and fracture rates. One of three cohorts reported an inverse association between serum 25(OH)D concentrations and fracture rates, and nine of twelve case-control studies found significantly lower 25(OH)D concentrations in cases versus controls. Differences in results may be attributed to whether all relevant confounders were controlled for and differences in baseline serum 25(OH)D concentrations. Other factors may also contribute to the heterogeneity, such as diagnosis of fractures.

Ottawa EPC Report: Falls - Postmenopausal women or elderly men.

Overall, there is fair evidence of an association between lower serum 25(OH)D concentrations and an increased risk of falls in institutionalized elderly. One study suggested a serum 25(OH)D concentration below 39 nmol/L was associated with an increased risk of falls.

Five studies (one RCT, three cohorts and one case-control) evaluated the association between serum 25(OH)D concentrations and risk of falls. One RCT, two of the three cohorts and one case-control study reported an inverse association between serum 25(OH)D concentrations and a risk of falls. In one cohort with a low percentage of vitamin D deficient participants, the association did not persist after adjustment for age and illness severity. In another cohort with an undetermined proportion of vitamin D deficient participants no significant association between serum 25(OH)D concentrations and risk of falls was observed. One case-control study reported no significant association between serum 25(OH)D concentrations and risk of falls after adjusting for serum PTH.

Ottawa EPC Report: Performance measures - Postmenopausal women or elderly men.

Overall, there is inconsistent evidence for an association of serum 25(OH)D concentrations with performance measures. In studies that reported an association, specific concentrations below which, declines in performance measures were increased, ranged from 50 to 87 nmol/L.

Seven studies (three RCTs and four cohorts) assessed the relation between 25(OH)D concentrations and performance related measures. Two of the three RCTs and two of the four cohorts reported an association between 25(OH)D concentrations and performance measures. The other studies did not find an association between 25(OH)D concentrations and performance measures.

Additional RCTs published after the Ottawa EPC report.

We identified three additional RCTs (published after the Ottawa EPC report)[80-82] that examined the effect of either vitamin D_2 or D_3 supplementation on total fractures, falls, or performance in elderly populations (≥71 years old). All three RCTs were rated C. In two of the three RCTs[80,81] calcium supplementation (800 or 1200 mg/d) was given to all participants. Baseline serum 25(OH)D concentrations were less than 40 nmol/L. The other RCT did not provide any information on background calcium intake or baseline serum 25(OH)D concentrations.[82] All three RCTs reported no significant reduction in the risk of total fracture or falls in elderly populations at daily vitamin D doses ranging from 400 IU to 822 IU.[80-82] Only one of the three new RCTs among elderly reported data on performance measures. Vitamin D supplementation (400 IU/d) improved gait speed and body sway in healthy elderly subjects.[80]

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data
- **51 – 70 y** The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report
- **≥71 y** Findings from three new RCTs did not show significant effects of either vitamin D_2 or D_3 supplementation (daily doses ranged from 400 IU to 822 IU) in reducing the risk of total fractures or falls among men and women in this life stage.
- **Postmenopause** The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report
- **Pregnant & lactating women** Not reviewed

Table 35. Vitamin D and bone health: Characteristics of RCTs published after the Ottawa EPC report

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lyons 2007[82] South Wales, UK (52°N) [17473911]	• Health status • Mean age (range), y • Male (%)	Living in care facilities including some elderly with mobility, cognitive, visual, hearing or communication impairments 84 (62-107) 23.7	nd	Vit D_2 100,000 IU 4-monthly vs. placebo	80% (percentage of occasions observed to take tablets)	
Burleigh 2007[81] Scotland (55° 57'N) [17656420]	• Health status • Mean age (SD), y • Male (%)	Inpatient with high levels of comorbidity, mortality and polypharmacy 83 (7.6) 40	25(OH)D: 22.0 nmol/L	Vit D_3 800 IU/d + Ca carbonate 1200 mg/d vs. Ca carbonate 1200 mg	Ca group=87%, Vit D+Ca group=89% (total study drug taken/total study drug prescribed, as recorded in drug prescription charts)	
Bunout 2006[80] Chile (32°S) [16797903]	• Health status • Mean age (SD), y • Male (%)	Healthy 76 (4) 11.6	25(OH)D: ≤40 nmol/L	Ca 800 mg/d vs. Ca 800 mg/d + Vit D 400 IU/d (with and without exercise training)	92% (tablet counting)	

Table 36. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lyons 2007[82] [17473911]	≥71 both sexes	First fracture	1°	Median time to first fracture = 387 (IQR: 220–582) d in Vit D_2 group; 367 (IQR:139–618) d in placebo group	Vit D_2 ~822 IU[A]	205	1670	HR Vit D/placebo	0.95	0.79, 1.15	NS	C
					Placebo	218	1673					
Burleigh 2007[81] [17656420]	≥71 both sexes	Fall	1°	Median 1 (IQR 15–71 d)	Vit D_3 800 IU + Ca carbonate 1200 mg	36	100	RR (Vit D+Ca)/Ca	0.82	0.59, 1.16	NS	C
					Ca carbonate 1200 mg	45	103					
		Fracture	1°	Median 1 (IQR 15–71 d)	Vit D_3 800 IU + Ca carbonate 1200 mg	1	100	nd	nd		NS	
					Ca carbonate 1200 mg	3	103					
Bunout 2006[80] [16797903]	≥71 both sexes	Fall	2°	9 mo	Ca 800 mg	13[B]	24	Fall free survival curve	nd		NS	C
					Ca 800 mg + exercise training	6[B]	22					
					Vit D 400 IU + Ca 800 mg	9[B]	24					
					Vit D 400 IU + Ca 800 mg + Exercise training	8[B]	22					

[A] Daily dose was calculated from the intermittent doses that were used in the study (i.e., 100,000 IU tablets every 4 months)
[B] Estimated from figure

Vitamin D and all-cause Mortality

Synopsis.

This synopsis is based on our reanalysis of a systematic review of RCTs on vitamin D supplementation for mortality.[i] In addition, it summarizes four observational studies on the association of vitamin D and all-cause mortality.

Three RCTs from the previous systematic review and an additional C rated RCT were included in our reanalysis. Three used daily doses that ranged between 400 and 880 IU, and one used 100,000 IU every 3 months. Our meta-analysis of the 4 RCTs (13,833 participants) shows absence of significant effects of vitamin D supplementation on all-cause mortality (RR = 0.97, 95 percent CI: 0.92, 1.02; random effects model). There is little evidence for between-study heterogeneity in these analyses.

One cohort study (rated B for methodological quality) found a significant trend for lower odds for death with increasing 25(OH)D concentrations. Three other cohort studies did not find a significant association between 25(OH)D concentrations and all-cause mortality. These three studies were rated C for their methodological quality.

The above are applicable to older (50-70 y) and elderly (≥71 y) men and women (mean age was >70 y in the included studies).

Detailed presentation (Tables 37, 38 & 39).

As mentioned in the Methods section, we updated and reanalyzed published meta-analyses of mortality outcomes. We drew our own conclusions based on our analyses. We also comment on the concordance of our conclusions with those of the published meta-analyses.

Relevant published systematic reviews of RCTs (with meta-analyses).

We identified two systematic reviews (with meta-analyses) of RCTs that summarized the effect of vitamin D supplementation with or without calcium on mortality.[83,84] One systematic review (Avenell 2008) examined only trials on fall prevention, and briefly described results on mortality.[84] The second meta-analysis (Autier 2007) focused specifically on mortality.[83] It included all RCTs identified in the first, as well as additional trials (which were not eligible for the primary analysis of the Avenell 2008 systematic review, namely prevention of falls).[83] Therefore, the Autier 2007 meta-analysis was used as the basis for our reanalysis.

Table 37 summarizes the findings of the Autier 2007 systematic review.

[i] Numerical data were extracted from previous systematic reviews –no additional studies were identified. For this reason, we did not appraise studies for their methodological quality.

Table 37. Summary of systematic review on vitamin D supplementation and all-cause mortality

Author Year [PMID]	Autier 2007[83] [17846391]
Design (Search Years)	Randomized controlled trials (1992-2006)
Population	Community dwelling or institutionalized adults
Intervention (Exposure) and Comparator	Supplementary vitamin D (at least 1000 mg/d) without calcium vs. placebo or no treatment
Results	18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (± calcium) supplementation Statistically homogeneous In our reanalysis we and excluded 3 of 18 trials and separated studies with vitamin D only from those with vitamin D and calcium combination. For details and results of our reanalysis, see text.
Comments	See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail.

AMSTAR Criteria

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	No	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores)	

Additional identified RCTs (not included in published systematic reviews).

Lyons 2007 (n=3343, 24 percent males) used monthly supplementation with 100,000 IU of vitamin D_2, orally for 3 years.[82] The trial took place in South Wales (latitude ~52°N) and included older people (mean age 84 y) living in sheltered accommodation. The primary outcome was prevention of fractures. The Lyons 2007 RCT received grade "C" for the all-cause mortality outcome, because of inconsistencies in the reported data. This RCT is included in the reanalysis described below.

Reanalysis.

We excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,[85] one was published only in abstract form,[86] in one trial the controls also received supplementation with vitamin D, albeit with a smaller dose,[87] and two trials used vitamin D injections.[88,89] One additional eligible RCT (Lyons 2007)[82] was identified and included in our meta-analysis.

Overall, four trials (13,899 patients) used only vitamin D supplementation without calcium. Among the four trials, sample sizes ranged from 2578 to 5292 participants. Followup periods ranged from 36 to 60 months. Vitamin D doses in most trials ranged between 400 and 830 IU per day.

Overall, there were no significant effects of vitamin D supplementation on mortality. The RR was 0.97 (95 percent CI 0.92, 1.02), with no evidence for between-study heterogeneity (P=0.39, I^2=0 percent).

Cohort studies.

We identified four prospective cohort studies described in 5 publications.[47,90-93] The characteristics of the four cohorts are shown in **Table 38**. One was rated "B" [90] for methodological quality and the remaining were rated "C".

Table 39 summarizes the findings of the four studies. Briefly, only Jia 2007[90] found a statistically significant trend between increasing 25(OH)D concentrations and lower odds for all-cause mortality (P=0.03). However, none of the odds ratios of the different 25(OH)D categories was significant, and if anything, they suggest an U shaped relationship between 25(OH)D and

mortality. All other cohorts did not find significant associations. Melamed 2008[47] performed analyses in subgroups of men and women, and <65 or ≥65 years of age, and found no significant associations (Table 33).

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** A subgroup analysis of people younger than 65 years in NHANES III (Melamed 2008) found no significant associations between 25(OH)D concentrations and all cause mortality.
- **51 – 70 y** Overall, there were no significant effects of vitamin D supplementation on mortality.
    - In a random effects model meta-analysis of five RCTs (n=13,899) the summary RR was 0.97 (95 percent CI 0.92, 1.02), with no evidence for between-study heterogeneity (p=0.39, I^2=0 percent). The mean participant age was more than 70 years in these RCTs.
    - Overall, data from four cohorts suggest no association between baseline 25(OH)D measurements and all-cause mortality (one cohort found a statistically significant trend for). A subgroup analysis of people aged 65 years or older in NHANES III (Melamed 2008) found no significant associations between 25(OH)D concentrations and all cause mortality.
- **≥71 y** The above (51–70 y) are applicable.
- **Postmenopause** No data
- **Pregnant & lactating women** No data

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle
Jia 2007[90] UK (57°N) [17442130]	• Health status • Age range, y • Male (%)	Not terminally ill or demented >75 52	• Assay method • Season blood drawn	RIA ND	Comparison of various 25(OH)D concentration categories		X		X	X	X
Shambrook 2004 & 2006[91,92] FREE[A] Australia (33°S) [15531500 & 16598375]	• Health status • Age range, y • Male (%)	Not bedridden >65 22	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Association with log 25(OH)D		X		X		
Visser 2006[93] Longitudinal Aging Study Netherlands (52°N) [16960177]	• Health status • Age range, y • Male (%)	General population[B] >65 51	• Assay method • Season blood drawn	Competitive protein binding ND	Comparison of various 25(OH)D concentration categories		X	X			X
Melamed 2008[47] NHANES III US (various) [18695076]	• Health status • Age mean (range), y • Male (%)	General population 45 (>=20) 46	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Comparison of various 25(OH)D concentration categories	X	X	X	X	X	X

[A] Fracture Risk Epidemiology in the Elderly
[B] ~40% with CVD and ~60% arthritis

Table 39. Vitamin D and all-cause mortality: Results of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Age range, sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Jia 2007[90] UK (57°N) [17442130]	>75, both sexes	Mortality	69	25(OH)D	6.0-23.0 (M)/ 7.0-19.0 (F)	41	75	1.74	0.91, 3.34	0.03	B
					23.1-30.0 (M)/ 29.1-24.0 (F)	34	86	1.40	0.73, 2.70		
					30.1-37.0 (M)/ 24.1-30.2 (F)	21	80	0.90	0.45, 1.79		
					37.1-47.0 (M)/ 30.3-39.0 (F)	17	78	0.80	0.39, 1.62		
					47.1-82.0 (M)/ 39.1-82.0 (F)	16	79	**1.00**	**Reference**		
Shambrook 2004 & 2006[91,92] FREE[A] Australia (33°S) [15531500 & 16598375]	>65, both sexes	Mortality	27	25(OH)D	NA	559	1112	0.87[B]	0.75, 1.01	nd	C
Visser 2006[93] Longitudinal Aging Study Netherlands (52°N) [16960177]	>65, both sexes	Mortality	72	25(OH)D	<25	66	127	1.28	0.85, 1.92	0.19	C
					25-49.9	42	462	1.00	0.72, 1.40		
					50-74.9	30	440	0.91	0.65, 1.26		
					≥75	29	231	**1.00**	**Reference**		
Melamed 2008[47] NHANES III US (various) [18695076]	>20, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.08, 1.46	nd	C
					17.8-24.3	nd	nd	1.06	0.89, 1.24		
					24.4-32.1	nd	nd	0.93	0.79, 1.10		
					>32.1	nd	nd	**1.00**	**Reference**		
Melamed 2008[47] NHANES III US (various) [18695076]	>20, men only	Mortality	104	25(OH)D	<17.8	nd	nd	1.04	0.83, 1.30	nd	C
					17.8-24.3	nd	nd	0.94	0.75, 1.19		
					24.4-32.1	nd	nd	0.82	0.64, 1.05		
					>32.1	nd	nd	**1.00**	**Reference**		

continued

Author Year Study Name Location (Latitude) [PMID]	Age range, sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Melamed 2008[47] NHANES III US (various) [18695076]	>20, women only	Mortality	104	25(OH)D	<17.8	nd	nd	1.55	1.15, 1.98	nd	C
					17.8-24.3	nd	nd	1.27	0.97, 1.66		
					24.4-32.1	nd	nd	1.16	0.87, 1.55		
					>32.1	nd	nd	**1.00**	**Reference**		
Melamed 2008[47] NHANES III US (various) [18695076]	20-65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.28	0.93, 1.76	nd	C
					17.8-24.3	nd	nd	1.13	0.81, 1.56		
					24.4-32.1	nd	nd	0.81	0.58, 1.14		
					>32.1	nd	nd	**1.00**	**Reference**		
Melamed 2008[47] NHANES III US (various) [18695076]	≥65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.03, 1.54	nd	C
					17.8-24.3	nd	nd	0.99	0.82, 1.20		
					24.4-32.1	nd	nd	0.97	0.79, 0.82		
					>32.1	nd	nd	**1.00**	**Reference**		

[A] Fracture Risk Epidemiology in the Elderly
[B] Per unit change in the log-transformed concentration.

Vitamin D and Hypertension and Blood Pressure

We searched for systematic reviews and primary studies that evaluated associations between vitamin D supplementation or serum concentrations and incidence of hypertension and change in blood pressure. For the outcome *incidence of hypertension*, we reviewed RCTs and other longitudinal studies. For the outcome *change in blood pressure*, we reviewed only RCTs. The EPC and the TEP agreed that due to the large volume of literature, the limited resources would not be expended on reviewing observational studies for the surrogate outcome blood pressure. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the "Pregnancy-related outcomes" section.

Hypertension.

Synopsis.

No systematic reviews evaluated the association between vitamin D intake or serum 25(OH)D concentrations and incidence of hypertension. A combined analysis of a small subset of the Health Professionals Follow-up (HPFS) and Nurses Health Studies (NHS) evaluated the association with serum 25(OH)D concentrations. The analysis found higher incidence of hypertension at 4 and 8 years in men with baseline 25(OH)D concentration less than 37.5 nmol/L (OR~3-6). In women, serum 25(OH)D concentrations less than 37.5 nmol/L also had a significantly higher incidence of hypertension at 4 years (OR~3), but not at 8 years (OR~1.5).

Detailed presentation (Tables 40 & 41).

One analysis (methodological quality B) evaluated the incidence of hypertension in a combined set of 613 men from the HPFS and 1198 women from the NHS who had serum 25(OH)D concentrations measured.[94] The men were on average 65 years old and the women 57 years old. Among the men at 4 years, those with serum 25(OH)D concentrations less than 37.5 nmol/L were significantly more likely to have new onset hypertension than either men with 25(OH)D concentrations above 75 nmol/L (OR=6.1) or above 37.5 nmol/L (OR=5.7). The association remained significant at 8 years, although with a smaller effect size (OR=3.5 and 3.0, respectively). In women, a similar, though weaker, effect was seen at 4 years, such that those with 25(OH)D concentrations less than 37.5 nmol/L were significantly more likely to have new onset hypertension than either women with 25(OH)D concentrations above 75 nmol/L (OR=2.7) or above 37.5 nmol/L (OR=3.0). However, this effect was smaller and nonsignificant at 8 years (OR=1.7 and 1.4, respectively). The study was limited primarily by its inclusion of only a relatively small subset of participants and its reliance on self-reported hypertension without assessment of blood pressure measurements.

In the second analysis by the same investigators, the NHS 2 study was analyzed for the association between serum 25(OH)D concentration and hypertension as a nested case-control study.[95] These women were on average 43 years old. Cases and controls (per the 2005 biennial questionnaire) were chosen from among those women without hypertension, cardiovascular disease, diabetes, obesity, or cancer at baseline (blood samples drawn from 1997 to 1999). After approximately 7 years, a statistically significant trend was found such that women in the three quartiles with serum 25(OH)D concentrations of 80.5 nmol/L or less were about 50 to 60 percent more likely to develop hypertension than those women with higher serum concentrations of 25(OH)D (adjusted OR = 1.52 to 1.66, each of which was statistically significant compared to

the highest quartile). The study was graded methodological quality B for similar reasons as the analysis of the HPFS and NHS studies.

Findings per vitamin D concentration.

The HPFS and NHS studies were analyzed with 25(OH)D cutpoints of 37.5 and 75 nmol/L. Significant associations were found for those with serum concentrations below 37.5 nmol/L. The NHS 2 study was analyzed with 25(OH)D quartiles, such that significant associations were found for those with serum concentrations of 80.5 nmol/L or less.

Findings per age and sex.

See above *Detailed presentation* of the HPFS and NHS for the separate analyses by sex. No subgroup analyses were reported by life stage. The participants in the studies were approximately 40 to 80 years old.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The NHS 2 included all women within the life stage. After approximately 7 years, those with serum 25(OH)D concentrations of 80.5 nmol/L or less were about 50 to 60 percent more likely to develop hypertension.
- **51 – 70 y** HPFS and NHS included participants mostly within this life stage. In men and women, the study found higher incidence of hypertension at 4 years followup in those with serum 25(OH)D concentrations less than 37.5 nmol/L; at 8 years, the association was significant only for men.
- **≥71 y** A minority of the men and few of the women appear to have been in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Postmenopause** The majority of the women in NHS were postmenopausal. A significant association between serum 25(OH)D concentrations less than 37.5 nmol/L and increased hypertension was found at 4 years, but not 8 years followup.
- **Pregnant & lactating women** Not reviewed

Table 40. Vitamin D and hypertension: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Forman 2007[94] HPFS, NHS US (various) [17372031]	• Health status • Mean age (SD), y • Male (%)	Any Men 65 (8) Women 57 (7) 34	• Assay method • Season blood drawn	RIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)		X	X			X	
Forman 2008[95] NHS 2 US (various) [18838623]	• Health status • Mean age (SD), y • Male (%)	No HTN, CVD, DM, obesity, cancer 43 (40-46) 0	• Assay method • Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)	X	X	X		X		

Table 41. Vitamin D and hypertension: Results of cohort and nested case control studies

Author Year Study Name [PMID]	Mean (SD) Age, Sex	Outcome (n/N; Incidence)	Followup Duration	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Men											
Forman 2007[94] HPFS [17372031]	65 (8), Men	Hypertension (61/613; 0.100)	4 y	25(OH)D	<37.5	6	33	6.13	1.00, 37.8*	nd	B
					37.5-75	33	247	1.12	0.51, 2.48		
					≥75	22	233	**1**	**Reference**		
					<37.5	6	33	5.68	1.01, 32.3*	<0.05	
					≥37.5	55	580	**1**	**Reference**		
		Hypertension (131/613; 0.214)	8 y	25(OH)D	<37.5	9	33	3.53	1.02, 12.3*	nd	
					37.5-75	nd	247	nd	nd		
					≥75	nd	233	**1**	**Reference**		
					<37.5	9	33	3.03	0.94, 9.76	NS	
					≥37.5	124	580	**1**	**Reference**		
Women											
Forman 2008[95] NHS 2 [18838623]	43 (40-46, range), Women	Hypertension (742 cases; 742 controls) Nested case control	~7 y	25(OH)D	41.75 (15.5-52.5)	208	371	1.66	1.11, 2.48	0.01	B
					59.5 (52.75-66.25)	188	370	1.55	1.07, 2.23		
					73.0 (66.5-80.5)	195	374	1.52	1.06, 2.18		
					94.75 (80.75-224)	151	369	**1**	**Reference**		
Forman 2007[94] NHS [17372031]	57 (7), Women	Hypertension (129/1198; 0.108)	4 y	25(OH)D	<37.5	11	nd[A]	2.67	1.05, 6.79*	nd	B
					37.5-75	60	nd	0.85	0.53, 1.34		
					≥75	58	nd	**1**	**Reference**		
					<37.5	11	nd	2.98	1.24, 7.20*	<0.05	
					≥37.5	118	nd	**1**	**Reference**		
		Hypertension (274/613; 0.229)	8 y	25(OH)D	<37.5	20	nd[A]	1.70	0.92, 3.16	nd	
					37.5-75	nd	nd	nd	nd		
					≥75	nd	nd	**1**	**Reference**		
					<37.5	20	nd	1.42	0.79, 2.56	NS	
					≥37.5	254	nd	**1**	**Reference**		

* Statistically significant (P<0.05)
[A] Due to formatting error in study table, no data on numbers of women in each category.

Vitamin D and blood pressure.

Synopsis.

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and changes in blood pressure. Three trials from Germany, UK, and India compared different doses of vitamin D (800 IU daily, a single dose of 100,000 IU, or 120,000 IU every 2 weeks) with placebo, with or without supplemental calcium in both groups. The study participants also varied: either older men, older men and women, or men mostly in their 40s. Both recruited older adults (over 63 or 70 years). All trials reported no significant effect on diastolic blood pressure. The A quality British study of a single dose of vitamin D 100,000 IU found no difference in systolic blood pressure after 5 weeks. The B quality German study found a significant net reduction of 7 mm Hg after 8 weeks in older women taking vitamin D 800 IU daily. The B quality Indian study of obese men mostly in their 40s, found a nearly significant net increase of 4 mm Hg after 6 weeks of vitamin D 120,000 IU every 2 weeks. No long term data were available.

Detailed presentation (Tables 42 & 43).

The A quality trial of single-dose vitamin D, performed in Cambridge, UK, recruited older adults (63 to 76 years, mean 70 years) who were not taking antihypertensive medications.[96] During the winter, they were given either a one-time dose of vitamin D_3 (100,000 IU [2.5 mg]) or placebo, and blood pressure was rechecked at 5 weeks. In both study arms, systolic and diastolic blood pressures fell by equal amounts, resulting in no net difference between vitamin D supplemented and placebo groups. No subgroup analyses were reported.

The German B quality trial of supplementation with combined vitamin D and calcium versus calcium alone recruited older women (70 to 86 years) without severe hypertension.[97] For 8 weeks, the women took either vitamin D_3 800 IU and calcium carbonate 1200 mg or calcium carbonate 1200 mg alone daily. Systolic blood pressure decreased by 13 mm Hg in those supplemented with vitamin D and calcium compared with a 6 mm Hg decrease in those taking calcium alone (P=0.02). Diastolic blood pressure declined by 7 mm Hg in both groups. No subgroup analyses were reported. The study was limited by inadequate reporting of its study methods and lack of blinding.

The Indian B quality study compared every other week vitamin D_3 supplementation 120,000 IU with placebo for 3 weeks in generally healthy but obese men without hypertension.[51] The men who received the vitamin D supplements had a net increase in systolic blood pressure of 4 mm Hg, which was close to statistically significant (P=0.06), but no significant difference in diastolic blood pressure. The study was limited by a high dropout rate (26 percent).

Findings per intake level.

No conclusions can be reached about an intake level threshold. In individual trials, a single dose of 100,000 IU of cholecalciferol had no significant effect on systolic and diastolic blood pressure after 5 weeks, a daily dose of vitamin D_3 800 IU together with calcium significantly lowered systolic blood pressure more than calcium alone, but every other week vitamin D_3 120,000 IU resulted in a nearly statistically significant increase in systolic blood pressure.

Findings per age and sex.

No conclusions can be reached about differences in effect based on age or sex. The study of older women found a significant decrease in systolic blood pressure with relatively low dose

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** A single study of men in this life stage found a near significant increase in systolic blood pressure with vitamin D and no effect on diastolic blood pressure.
- **51 – 70 y** One trial included people with an average age of 70 years, implying that about half were within this life stage. No significant effect on blood pressure was found of a single large dose of vitamin D.
- **≥71 y** Both trials included people within this life stage. The trial of people with an average age of 70 years found no significant effect of a single large dose of vitamin D. The single trial of women over age 70 years found a significant benefit for systolic blood pressure for vitamin D_3 800 IU and calcium carbonate 1200 mg compared with calcium carbonate 1200 mg alone.
- **Postmenopause** The women in both trials were postmenopausal. See the ≥71 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 42. Vitamin D and blood pressure: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Scragg 1995[96] Cambridge, UK (52°N) [7498100]	• Health status • Mean age (range), y • Male (%)	No HTN 70 (63-76) 46%	25(OH)D: 34.5 nmol/L (treatment group), 32.25 nmol/L (control group)	Vit D_3 100,000 IU (2.5 mg) one-time dose vs. Placebo	nd	Complete trial performed in winter
Pfeifer 2001[97] Lower Saxony, Germany (52°N) [11297596]	• Health status • Mean age (range), y • Male (%)	Healthy, low Vit D 75 (70-86) 0	25(OH)D < 50 nmol/L	Vit D_3 + Ca supplement vs. Ca supplement	95±12% for the Ca tablets and 96±10% for the Vit D_3 + Ca tablets (pill counting)	
Nagpal 2009[51] New Delhi, India (28.5°N) [19125756]	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 44 (8) 100%	25(OH)D: 36.5 nmol/L (treatment group), 30.0 nmol/L (control group)	Vit D_3 120,000 IU every 2 weeks vs. Placebo	100% (implied); supervised home visits	Excluded subjects who refused subsequent blood draws

Table 43. Vitamin D and blood pressure: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Scragg 1995[96] UK [7498100]	63-76 y, Both	SBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	149	-5	-14.4, 4.4[A]	0	-4.2, 4.2[A]	0.81	A
					Placebo	94		147	-5	-17.9, 7.9[A]				
Pfeifer 2001[97] Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	144.1	-13.1	nd	-7.4	-13.6, -1.2[A]	0.02	B
					Ca carbonate 1200 mg	72		140.6	-5.7	nd				
Nagpal 2009[51] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	124	+0.6	-2.7, 3.9	+4.0	-0.02, 8.0	0.06	B
					Placebo	36		124	-3.4	-5.8, -1.0				
DIASTOLIC BLOOD PRESSURE														
Scragg 1995[96] UK [7498100]	63-76 y, Both	DBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	82	-1	-6.8, 4.8[A]	0	-2.8, 2.8[A]	0.92	A
					Placebo	94		82	-1	-6.8, 4.8[A]				
Pfeifer 2001[97] Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	84.7	-7.2	nd	-0.3	-0.7, -0.1[A]	0.10	B
					Ca carbonate 1200 mg	72		82.6	6.9	nd				
Nagpal 2009[51] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	78	+0.4	-2.1, 3.0	+1.7	-1.5, 4.9	0.31	B
					Placebo	36		77	-1.3	-3.2, 0.7				

[A] Estimated from available data

Vitamin D and Bone Mineral Density or Bone Mineral Content

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC (Table 28).[6] Because the Ottawa's EPC report did not have separate analyses on the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation are presented in "Combined vitamin D and Calcium" section.

The Ottawa EPC report was updated with literature published between January 2006 and September 2008, selected according to our eligibility criteria. For adults, we included only bone mineral density (BMD) indices. For children, we included only bone mineral content (BMC) indices. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis.

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). Furthermore, Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck in postmenopausal women and elderly men. However, there was discordance between the results from RCTs and the majority of observational studies.[6] Three new RCTs identify from our updated search all showed no significant effects of vitamin D supplementation on BMC or BMD in children or adults, respectively.

Our updated search did not identify any new RCTs examining the effect of vitamin D on BMD and related outcomes in pregnant or lactating women.

Detailed presentation (Tables 44 & 45).

Ottawa EPC Report: Bone mineral content - Infants (0 through 12 months).

Overall, there is inconsistent evidence for an association between a specific serum 25(OH)D concentration and the bone health outcome BMC in infants. Of the two RCTs examining BMC, one demonstrated no significant benefit of higher serum 25(OH)D concentrations on radial bone mass while the other showed a transient increase of BMC compared to the unsupplemented group at 12 weeks but not 26 weeks. Of the three case-control studies, greater whole body BMC, was related to higher serum 25(OH)D concentrations.

Ottawa EPC Report: Bone mineral content or density - Older children (6 months through before puberty) and adolescents (the onset of puberty through 18 years).

Overall, there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. However, the results from two RCTs of vitamin D supplementation have not confirmed a consistent benefit on BMD or BMC across sites and age groups.

There were seven studies in older children and adolescents (two RCTs, three cohorts, one case-control and one before-after study) that evaluated the relationship between serum 25(OH)D concentrations and BMC or BMD. In older children, there was one RCT, one prospective cohort and one before-after study. One RCT did not find an association between serum 25(OH)D concentrations and distal radial BMC. Two of three studies found an association between lower baseline serum 25(OH)D concentrations and lower BMC or BMD. The effect of bone size and muscle mass on these outcomes in relation to baseline serum 25(OH)D concentrations was not reported. One RCT demonstrated a significant relation between baseline serum 25(OH)D

concentrations and baseline BMD of the lumbar spine, femoral neck and radius. However, only high dose supplementation with 14,000 IU/wk of vitamin D_3 increased BMC of the total hip.

Ottawa EPC Report: Bone mineral density – Postmenopausal women and elderly men.

Overall, there was discordance between the results from RCTs and the majority of observational studies that may be due to the limitations of observational studies to control for all relevant confounders. Five RCTs, and three cohort studies did not find an association between serum 25(OH)D concentrations and BMD or bone loss. Four cohort studies found a significant association between 25(OH)D concentrations and bone loss, which was most evident at the hip sites but the evidence for an association between 25(OH)D concentrations and lumbar spine BMD was weak. Six case-control studies suggested an association between 25(OH)D concentrations and BMD and the association was most consistent at the femoral neck BMD.

Based on the results from the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. Specific circulating concentrations of 25(OH)D below which bone loss at the hip was increased ranged from 30-80 nmol/L.

Ottawa EPC Report: Bone mineral density - pregnant or lactating women.

One cohort study did not find an association between serum 25(OH)D concentrations and change in BMD that occurred during lactation. Limitations in the study design and sources of bias highlight the need for additional research on vitamin D status in pregnancy and lactation, and the association with bone health outcomes.

Additional studies published after the Ottawa EPC report.

One A quality RCT compared the effect of vitamin D_2 supplementation on hip BMC in 256 elderly women between 70 and 90 years of age.[98] All elderly women in this trial had normal physical functioning. They were randomly assigned to receive either vitamin D_2 (1000 IU/d) plus calcium (1200 mg/d) supplement or calcium (1200 mg/d) supplement alone for one year. The mean baseline dietary calcium intake was 1097 mg/d and mean 25(OH)D concentration was 44.3 nmol/L. Total hip BMD increased significantly in both groups, with no difference between the vitamin D_2 plus calcium and calcium alone groups (hip BMD change: vitamin D, +0.5 percent; control, +0.2 percent).

One B quality RCT analyzed 89 and 83 healthy adult women and men separately.[99] The participants were Pakistani immigrants living in the Copenhagen area of Denmark (latitude 55 N°). Women and men were randomly assigned to receive either daily dose of 400 IU or 800 IU vitamin D_3, or placebo for one year. For women, the mean baseline dietary calcium intake was 495 mg/d and mean 25(OH)D concentration was 12 nmol/L. For men, the mean baseline dietary calcium intake was 548 mg/d and mean 25(OH)D concentration was 21 nmol/L. At the end of study, in both women and men, there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.

Two RCTs, both rated C, compared the effect of vitamin D supplementation on BMC in healthy girls, aged between 10 and 17 years old.[35,99] First RCT analyzed 26 healthy girls, who were Pakistani immigrants primarily living in the Copenhagen area Denmark (latitude 55 N°).[99] Girls were randomly assigned to receive either daily dose 400 IU or 800 IU vitamin D_3, or placebo for one year. The mean baseline dietary calcium intake was 510 mg/d and mean 25(OH)D concentration was 11 nmol/L. At the end of study, there were no significant differences in whole body BMC changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups. Second RCT analyzed 168 healthy girls, living in the Greater

Findings by life stage.

- **0 – 6 mo** The Ottawa EPC report concluded that there is inconsistent evidence for an association between a specific serum 25(OH)D concentration and the bone health outcome BMC in infants. There were no new data since the Ottawa report.
- **7 mo – 2 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **3 – 8 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **9 – 18 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. Two new RCTs enrolled only girls in this life stage. The results showed no significant differences in whole body BMC changes between either lower doses of vitamin D (200 or 400 IU/d) or higher dose of vitamin D (800 or 2000 IU/d) and the placebo groups.
- **19 – 50 y** The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled primarily men and women in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.
- **51 – 70 y** The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled some men in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.
- **≥71 y** The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to

support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled only elderly women in this life stage. The results showed that vitamin D_2 supplementation (1000 IU/d) had no additional effect on hip BMD compared to calcium supplementation alone.

- **Postmenopause** There were no new data since the Ottawa report.
- **Pregnant & lactating women** There were no new data since the Ottawa report.

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Zhu 2008[98] Perth, Australia (32 °S) [18410225]	• Health status • Mean age (SD), y • Male (%)	nd (based on the inclusion and exclusion criteria, assume subjects were not very healthy but normal physical functioning) 77 (4.5) 0	25(OH)D: 44.3 nmol/L Ca: 1097 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. Ca citrate 1200 mg/d	86.7% and 86.8% in the vitamin D and the control groups (tablet counting)	
Andersen 2008[99] Copenhagen, Denmark (55 N°) [18208636]	• Health status • Mean age (range), y • Male (%)	Healthy Adolescent girls: 12.2 (10.1-14.7) Women: 36.2 (18.1-52.7) Men: 38.3 (17.9-63.5) 42	25(OH)D: Adolescent girls: 11 nmol/L Women: 12 nmol/L Men: 21 nmol/L Ca: Adolescent girls: 510 mg/d Women: 495 mg/d Men: 548 mg/d	Vit D3 400 IU/d, or Vit D3 800 IU/d vs. placebo	The median compliance was 85 (range 43-100), 92 (42-115) and 93 (33-105)% for girls, women, and men, respectively (pill counting)	Pakistani, living in Denmark. Compliance was lower for girls.
El-Hajj 2006[35] Beirut, Lebanon (33°53'N) [16278262]	• Health status • Mean age (range), y • Male (%)	Healthy 13.2 (10-17) 0	25(OH)D: 34.9 nmol/L Ca: 677 mg/d	Weekly oral Vit D doses of 1400 IU (=Vit D 200 IU/d) or 14,000 IU (Vit D 2000 IU/d) vs. placebo	Placebo - 98%, Low dose group - 98%, High dose group - 97% (pill counting)	

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu 2008[98] Perth, Australia (32 °S) [18410225]	71+. Women only	Hip BMD	1°	12	Vit D_2 1000 IU + Ca citrate 1200 mg	123	mg/cm^2	851	0.5%	-0.09, 1.09	0.3%	nd	NS	A
					Ca citrate 1200 mg	133		826	0.2%	-0.19, 0.59				
Andersen 2008[99] Copenhagen, Denmark (55 N°) [18208636]	18-53, Women only	Lumbar spine BMD	1°	12	Vit D_3 400	30/21[A]	mg/cm^2	1.06	0%	nd	-1%	nd	NS	B
					Vit D_3 800	30/21		0.98	1%	nd	0%	nd	NS	
					Placebo	29/18		0.99	1%	nd				
Andersen 2008[99] Copenhagen, Denmark (55 N°) [18208636]	18-64, Men only	Lumbar spine BMD	1°	12	Vit D_3 400	25/19[A]	mg/cm^2	1.03	2%	nd	0%	nd	NS	B
					Vit D_3 800	31/26		0.92	7%	nd	5%	nd	NS	
					Placebo	27/19		1.03	2%	nd				
Andersen 2008[99] Copenhagen, Denmark (55 N°) [18208636]	10-15 y girls	BMC	1°	12	Vit D_3 400	9/7[A]	kg	1.3	22%	nd	7%	nd	NS	C[B]
					Vit D_3 800	9/7		1.5	10%	nd	-5%	nd	NS	
					Placebo	8/7		1.7	15%	nd				
El-Hajj 2006[35] Beirut, Lebanon (33°N) [16278262]	10-17 y girls	BMC	1°	12	Vit D 2000 IU	55	kg	1.2	6.2%	4.7, 7.7	0.1%	-1.1, 2.0[C]	NS	C
					Vit D 200 IU	58		1.1	6.1%	4.6, 7.6	1.1%	-0.8, 3.2[C]	NS	
					Placebo	55		1.1	5.0%	3.8, 6.2				
	Subgroup–Premenarcheal girls, mean age 10 y	BMC	1°	12	Vit D 2000 IU	14	kg	0.8	11.6%	9.4, 13.8	4.2%	0.7, 7.7[C]	NS	
					Vit D 200 IU	12		0.7	11.4%	9.1, 13.7	4.0%	0.5, 7.5[C]	NS	
					Placebo	8		0.8	7.4%	4.7, 10.1				

[A] Baseline/final sample size
[B] Downgraded to C because very small sample size (insufficient power) and no adjustments for confounders
[C] Estimated from available data

Calcium and Health Outcomes

Calcium and Growth

We reviewed systematic reviews and primary studies that evaluated relationships between calcium intake and growth parameters in infants and children.

Synopsis.

One systematic review and three primary studies evaluated supplemental intake of calcium and growth parameters in infants and children. The systematic review with a meta-analysis of 17 RCTs did not find an effect on weight and height gain attributable to calcium supplement in children ranging from 3 to 18 years of age. Three additional primary studies reported similar findings. Overall, the studies reviewed did not find a relationship between supplemental calcium intake and growth parameters.

Detailed presentation (Tables 46, 47 & 48).

0 - 6 months; 3 - 8 years; 9 - 18 years; pregnant women.

One systematic review of RCTs of supplemental calcium on bone related outcomes in children (age 3-18 y) also examined changes in height and weight at followup.[100] The systematic review (comprised of studies in Australia, China, Gambia, Israel, Switzerland, and US) conducted a meta-analysis of 17 RCTs with a total of 2088 subjects and found no significant difference in weight (weighted mean difference +0.14 kg (favors control)(95 percent CI -0.28, +0.57 kg)) and height gain (weighted mean difference +0.22 cm (favors control)(95 percent CI -0.30, +0.74 cm)) between those who were and those who were not supplemented. There was no significant statistical heterogeneity in the included studies. The calcium intake ranged from 300 to 1200 mg/d lasting from 0.7 to 4 years. The majority of the supplement used was calcium carbonate. This systematic review met seven of 11 AMSTAR[i] quality checklist items.

Two primary studies rated B in methodological quality and one primary study rated C provided additional information. One RCT from Denmark randomly assigned 110 girls (mean age 13 years) with either low (<713 mg/d) or medium (1000 to 1304 mg/d) habitual calcium intake to a supplement of calcium 500 mg/d (calcium carbonate) or placebo for 1 year.[101] There was no significant difference in height or weight gain among the groups at followup. One post hoc analysis of an RCT in Nebraska on bone mass analyzed 59 girls (mean age 9.5 years) who were randomly assigned to either a calcium enriched diet, supplying at least 1500 mg of calcium per day (~1656 mg/d), or usual diet (961 mg/d).[102] There was no significant difference in weight gain at 2 years followup. A cohort study in Washington DC analyzed dietary intake data from 322 pregnant African American women (mean age 21.6 years; 39 percent 16-19 years) and found that “none of the food energy and nutrient intakes [mean calcium intake 933 mg ± 52 (SE)] was significantly correlated with any of the pregnancy outcome measures”. No specific quantitative relationship between calcium intake and infant birth weight or length was reported.[103]

[i] A measurement tool to assess the methodological quality of systematic reviews

Findings by life stage.

- **0 – 6 mo** A cohort study of dietary intake in 322 pregnant African American women found that calcium intake was not significantly correlated with any pregnancy outcome measures, including infant birth weight or length.
- **7 mo – 2 y** No study covered this life stage.
- **3 – 8 y** One meta-analysis of 17 RCTs in children (age 3-18 y) found no significant difference in weight and height gain between those who were and those who were not supplemented at followup. The calcium intake ranged from 300 to 1200 mg/d lasting from 0.7 to 4 years.
- **9 – 18 y** In addition to the findings from the above meta-analysis, two primary studies provided additional information. One RCT of calcium 500 mg/d (calcium carbonate) versus placebo for 1 year found no significant difference in height or weight gain among the 110 girls (mean age 13 years) at followup. A post hoc analysis of an RCT of calcium enriched diet (~1656 mg/d) versus usual diet (~961 mg/d) on bone mass found no significant difference in weight gain at 2 years followup in 59 girls (mean age 9.5 years).
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed
- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** See 0 – 6 month results.

Table 46. Summary of systematic review of calcium on growth in children

Author Year [PMID]	Winzenberg 2007[100] [17636098]
Design (Search Years)	Randomized controlled trials (1966-2005)
Population	Children <18 y
Intervention (Exposure) and Comparator	Supplemental and dietary calcium 300-1200 mg/d vs. placebo
Results	17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity
Comments	Post hoc analysis performed on trials identified for a meta-analysis of randomized controlled trials of calcium on bone outcomes

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Unclear if all languages included; study quality assessed but not factored into the M-A	

Table 47. Calcium and growth: Characteristics of primary studies

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Lorenzen 2006[101] Denmark (55ºN) [16400044]	• Health status • Mean age (range/SD), y • Male (%)	no specific health issue reported 13 0	88-item FFQ (no internal validation); dietary calcium: 957 mg/d; 25(OH)D: 34.5 nmol/L	Ca CO_3 (Ca 500 mg/d) X 1 y vs. placebo	x	x	x				RCT; Danish surnames only
Lappe 2004[102] Omaha, NE US (41ºN) [15354150]	• Health status • Mean age (range/SD), y • Male (%)	healthy 9.5 0	3-d food record (no internal validation); dietary intake calcium: 819 mg/d; dietary vit D 180 IU/d (4.5 µg/d)	Calcium rich diet (~1656 mg/d) vs. usual diet (~961 mg/d); wt & ht change at 2 y	x	x	x			x	Post hoc of RCT on bone mass; 95% white, 5% black
Johnson 1994[103] Washington DC, US (38ºN) [8201444]	• Health status • Mean age (range/SD), y • Male (%)	pregnant; no DM, sickle, thalassemia, HbC disease 22 (39% 16-19) 0	FFQ (no internal validation); calcium 933.4 mg/d	Relationship between maternal calcium intake and birth weight, height							Cohort study; all African American; Total Ca (from food)

Table 48. Calcium and growth: Results of primary studies

Author Year Study Name PMID	Life Stage	Outcome	1°/2°	Mean Followup, Y	Interventions, Ca daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
RCT														
Lorenzen 2006[101] (55ºN) [16400044]	9-18 female	wt in medium Ca intake group (1000-1304 mg/d)	1º	1	500 mg/d x 1 y	30	kg	51.8	5.1	1.7, 8.5[A]	0.2	-4.4, 4.9[A]	NS	B
					Placebo	30	kg	50.7	4.9	1.8, 8.0[A]				
		wt in low Ca intake group (<713 mg/d)	1º	1	500 mg/d x 1 y	30	kg	52.2	4.1	0.7, 7.5[A]	1.1	-3.6, 5.8[A]	NS	
					Placebo	30	kg	49.5	3.0	-0.2, 6.2[A]				
		ht in medium Ca intake group (1000-1304 mg/d)	1º	1	500 mg/d x 1 y	30	cm	162.5	3.7	1.6, 5.8[A]	-0.3	-3.3, 2.8[A]	NS	
					Placebo	30	cm	161.9	4.0	1.7, 6.3[A]				
		ht in low Ca intake group (<713 mg/d)	1º	1	500 mg/d x 1 y	30	cm	159.6	3.6	1.1, 6.1[A]	0.5	-3.3, 4.3[A]	NS	
					Placebo	30	cm	160.1	3.1	0.3, 5.9[A]				
Post hoc analysis of an RCT on bone outcomes														
Lappe 2004[102] (41ºN) [15354150]	9-18 female	wt	2º	2	Ca enriched diet (~1656 mg)	27	kg	32.2	10.7	8.2, 13.2[A]	-0.2	-4.1, 3.7[A]	NS	B
					Usual diet (~961 mg)	32	kg	33.2	10.9	7.9, 13.9[A]				
		ht	2º	2	Ca enriched diet (~1656 mg)	27	cm	137	14	11.5, 16.5[A]	1	-2, 4[A]	NS	
					Usual diet (~961 mg)	32	cm	138	13	11, 15[A]				
Cohort														
Johnson 1994[103] (38ºN) [8201444]	9-18 female; infant 0-6 mo	birth wt & length	1º	until delivery	322 African American women with a mean dietary calcium intake of 933 mg/d; "None of the food energy and nutrient intakes was significantly correlated with any of the pregnancy outcome measures". No specific quantitative relationship between calcium intake and infant birth weight or length was reported.									C

[A] Estimated from reported data

Calcium and Cardiovascular Disease

Synopsis.

No qualified systematic reviews evaluated the association between calcium intake and incidence of cardiovascular disease. No calcium intervention trials evaluated cardiovascular outcomes. Ten longitudinal cohort studies and one nested case-control study analyzed associations with various specific cardiovascular events. In all studies, baseline calcium intake, assessed by food frequency questionnaires, were analyzed as predictors of long-term cardiovascular outcomes. We point out where there were "suggestions" of associations in cases where P values were about 0.10 and/or there were consistent, though not statistically significant differences in risk compared to the lowest risk category of at least 20 percent.

Notably, the implied ranges of calcium intake within studied populations varied widely across studies. At one extreme, men and women in the Japan CC study had mean calcium intakes in the lowest quintile of 250 or 266 mg/day and in the highest quintile of 665 and 667 mg/day. The Japan PHC study and the Taiwanese CVD-FACTS study had similarly low calcium intake. The study with the highest calcium intake was the ATBC study of men in Finland. Median calcium intakes in the lowest and highest quintiles were 876 and 1916 mg/day, respectively; the overall median intake was 1379 mg/day.

Cardiovascular death was analyzed in two large studies analyzed, separately in men and women. Neither found a significant association between calcium intake and cardiovascular death after 9 or 28 years in either men or women.

Combined fatal and nonfatal cardiac events were analyzed in two large and one relatively small studies, in either both sexes together or just men. None found a significant association between calcium intake and cardiac events after 10 to 13 years.

Cardiac death was analyzed in three large and one relatively small studies, separately in men and women. Overall, no consistent significant association between calcium intake and cardiac death after 8, 9, 12, or 28 years of followup was found in the various studies, in either men or women. One study (the Iowa WHS) found a significant association between calcium intake of less than 696 mg/day and higher risk of ischemic heart disease death in white women aged 55 to 69 years.

Nonfatal myocardial infarction was analyzed by one large study of men. No significant association was found with calcium intake after 12 years of followup.

Total strokes were analyzed in five large and one relatively small studies, in both sexes combined, and separately for men and women. The studies had disparate findings. A Japanese and a Taiwanese study of men and women (40-59 y and ≥40 y, respectively) found progressively lower risks for stroke in people in higher quintiles of calcium intake after 13 and 11 years, respectively, in the setting of overall relatively low dietary calcium intake. A small Finnish study of both men and women (65-99 y) found no significant association after 10 years. The two studies of men (40 to 75 years old) found suggestions of associations (not statistically significant), though with trends in opposite directions; one suggested the highest risk for stroke in men with calcium intake below approximately 750 mg/day after 8 years; one suggested the highest risk for cerebral infarctions in men with calcium intake above about 1000 mg/day after 14 years. The study of women (32-57 y) found a nonsignificant trend after 14 years, but significantly higher stroke risk in those with calcium intake less than about 500 mg/day compared with women in the next two higher quintiles of calcium intake.

Fatal strokes were analyzed in one large cohort study and a nested case-control study, separately in men and women. None found a significant association between calcium intake and cardiac events after 10 to 13 years of followup.

Detailed presentation (Tables 49 & 50, Figures 11 & 12).

Cardiovascular death.

Two longitudinal cohort studies analyzed risk of cardiovascular death (death from cardiac or cerebrovascular events), separately in men and women, according to quintiles.

In the Japan Collaborative Cohort (Japan CC),[104] about 23,000 men aged 40 to 79 years without a history of cardiovascular disease were followed for 8.9 years; 3 percent died of a cardiovascular event. Men within the calcium quintiles had mean calcium intakes that ranged from 250 to 665 mg/day. No significant association was found between calcium quintile and cardiovascular death risk. In a study of Dutch civil servants (and spouses),[105] 1340 men aged 40 to 65 years (regardless of cardiovascular history) were followed for 28 years. About 27 percent (age-adjusted) had a cardiovascular death. The calcium intake quintiles ranged from less than 585 mg/day to more than 1245 mg/day. No significant associations were found between calcium intake and risk of cardiovascular death; however, men in the lowest quintile (≤585 mg/day) had an adjusted odds ratio of cardiovascular death of 1.3 (95 percent CI 0.8, 1.9) compared to those in the highest quintile. Both studies had methodological quality B. The Japanese study did not define cardiovascular mortality and the Dutch study did not report a complete analysis of the calcium intake quintiles.

In the Japan CC, about 35,600 women aged 40 to 79 years without a history of cardiovascular disease were followed for 8.9 years; 1.8 percent died of a cardiovascular event. Women within the calcium quintiles had mean calcium intakes that ranged from 266 to 667 mg/day. No significant trend across quintiles or associations among quintiles was found for risk of cardiovascular death. However, women in the lowest quintile had about 25 to 30 percent lower risks of cardiovascular death than women in the next two higher quintiles. In the Dutch civil servants study, 1265 women were followed for 28 years. About 14 percent had a cardiovascular death. The calcium intake quintiles ranged from less than 445 mg/day to more than 850 mg/day. No significant associations were found between calcium intake and risk of cardiovascular death.

Cardiac events, total.

Three longitudinal cohort studies analyzed combined fatal and nonfatal cardiac events, including coronary heart disease, acute myocardial infarction, and ischemic heart disease; two combined both sexes, one included only men.

In the Japan Public Health Center (Japan PHC) study (methodological quality A),[106] about 41,500 people aged 40 to 59 years, without cardiovascular disease, were followed for 13 years; 0.8 percent had cardiac events. People within the calcium intake quintiles had median calcium intakes that ranged from 233 to 753 mg/day. No association was found between calcium intake and risk of coronary heart disease events. In a small Finnish longitudinal study,[48] 755 people aged 65 to 99 years, regardless of cardiovascular history were followed for 10 years; 17 percent had a cardiac event. No significant association was found between tertiles of calcium intake and all acute myocardial infarctions. This methodological quality C study did not report relevant data including information on the calcium intake within the tertiles.

In the Health Professionals Follow-up Study (HPFS),[107] about 39,000 men with a mean age of 54 years, without cardiovascular disease were followed for 12 years; 3.7 percent had an

ischemic heart disease event. The study was of methodological quality A. Men within the calcium quintiles had mean calcium intakes that ranged from 523 to 1377 mg/day. No significant association was found between calcium intake and risk of cardiac events.

Cardiac death.

Four longitudinal cohort studies analyzed death from cardiac events, separately in men (3 studies) and women (3 studies).

In the three studies of men, all found no significant association between calcium intake and cardiac death. All three studies are described above. In HPFS 1.1 percent of men died of a cardiac event during 12 years of followup.[107] In the Japan CC study 0.6 percent of men died of a cardiac event during 9 years of followup (methodological quality A for this outcome).[104] In the Dutch civil servants study about 15 percent (age-adjusted) died of a cardiac event during 28 years of followup.[105]

Three studies analyzed cardiac death in women. In two studies, both described above, there was no significant association between calcium intake and cardiac death. In the Japan CC study 0.3 percent of women died of a cardiac event during 9 years of followup.[104] In the Dutch civil servants study about 6 percent (age-adjusted) died of a cardiac event during 28 years of followup.[105] The Iowa Women's Health Study (Iowa WHS) analyzed about 34,500 white women, aged 55 to 69 years, without ischemic heart disease. During 8 years of followup, 1.1 percent died of a cardiac event. However, the study was of methodological quality B for this outcome because the outcome was not fully ascertained. The calcium intake quartiles ranged from less than 696 mg/day to more than 1425 mg/day. There was a suggestion of an association between lower calcium intake and higher risk of cardiac death, with a P value of 0.09 for the trend across quartiles and statistically significant adjusted relative risks of cardiac death for women with calcium intakes above 696 mg/day of 0.62 to 0.75 (compared to the lowest quartile).

Cardiac events, nonfatal.

Only the HPFS, described above, analyzed nonfatal cardiac events (methodological quality A).[107] During 12 years of followup 2.6 percent of almost 40,000 men had nonfatal myocardial infarctions. No significant association was found between calcium intake and nonfatal cardiac events.

Stroke, total.

Six longitudinal cohort studies analyzed combined fatal and nonfatal strokes, in either both sexes combined, or men and women separately.

In the Japan PHC study, described above (cardiac events, total), 3 percent of people suffered strokes during 13 years of followup (methodological quality A).[106] The study found a significant association between baseline calcium intake and risk of stroke. The risk of stroke was progressively lower in progressively higher quintiles of calcium intake. People with a median calcium intake of 439 mg/day (middle quintile) had a statistically significant adjusted hazard ratio (HR) of 0.79 compared to those with a median calcium intake of 233 mg/day. Those in higher quintiles had lower HRs; across quintiles, the trend had a P value of 0.02. As is evident from the median calcium intake levels within the quintiles, the middle-aged Japanese in this study had considerably lower average calcium intake than in most other studies (particularly those performed in the US). Compared to similar studies evaluated here, the calcium intake was approximately half of that in the HPFS or Iowa WHS. The CVD-FACTS study, performed in men and women at least 40 years old in Taiwan, evaluated ischemic strokes.[108] After a mean followup of 10.6 years, 7.4 percent of the cohort had an ischemic stroke. The B quality study

divided the cohort into tertiles. Similar to the Japanese study, the typical calcium intake was relatively low by Western standards (the average dietary calcium intake was approximately 520 mg/day). Those in the lower two tertiles had about a 50 percent increased risk of ischemic stroke than those in the highest tertile (>591 mg/day). While the adjusted OR for each tertile were not quite statistically significant (1.52 [95 percent CI 0.98-2.35] for lowest tertile; 1.49 [95 percent CI 0.99-2.24] for middle tertile; compared to highest tertile), the trend across tertiles had a P value of 0.03. The third study of combined men and women, of older Finns (described above under C*ardiac events, total*), found no significant association with stroke among 755 people followed for 10 years (stroke incidence 9.3 percent; methodological quality C).[48]

Both studies of men alone suggest trends across quintiles of calcium intake and stroke risk; however, the associations were in opposite directions. The HPFS, described above (cardiac events, total; methodological quality A) had a stroke incidence of 0.75 percent during 8 years of followup. Men in higher quintiles of calcium intake had generally lower adjusted relative risks (RR) of stroke compared to the lowest quintile (median calcium intake 500 mg/day); though none of the RRs was statistically significant and the P value for the trend across quintiles was 0.10. Notably, the RR of stroke for men in the middle quintile (median calcium intake 800 mg/day) was 0.72 (95 percent CI 0.50, 1.03); though the RRs for men in higher quintiles were closer to 1 with wider 95 percent confidence intervals. In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, performed in southern Finland, about 26,500 men aged 50 to 69 years without a history of stroke were followed for almost 14 years; 10 percent suffered a stroke. The study was of methodological quality C because there was large misclassification of stroke outcomes in a sample of subjects (5-21 percent). Men in the lowest quintile of calcium intake (median 876 mg/day) had the lowest adjusted RR for cerebral infarction. Men in all higher quintiles (medians ranging from 1178 to 1916 mg/day) all had RR of about 1.10 that were near statistical significance (e.g., 95 percent CI for highest quartile was 0.98, 1.26). The P value of the trend of association across quintiles was 0.09.

One study evaluated total strokes in women alone. The Nurses Health Study (NHS) evaluated about 86,000 women aged 32 to 57 years with no history of cardiovascular disease. The study was rated methodological quality A. During 14 years of followup 0.8 percent of women suffered a stroke. The women in the four quintiles above the lowest quintile (who had a median calcium intake of 395 mg/day) all had similar adjusted RR of stroke (0.71-0.87); the RRs of those women in the second and third quintiles were statistically significant. However, the trend of associations across quintiles was not statistically significant.

Stroke death.

One longitudinal cohort study (with subanalyses in men and women separately) and one nested case-control study (in men) evaluated fatal strokes.

Both studies of men found no significant association between calcium intake and risk of stroke death. In the Japan CC study (described above, methodological quality A for this outcome) 1.4 percent of men died of stroke during 9 years of followup. The second study was a nested case-control study performed in China. In a prospective cohort of about 18,000 men aged 45 to 64 years, regardless of cardiovascular history, 245 died of stroke (1.3 percent) during 12 years of followup. These cases were matched with 1225 controls. The remaining 17,000 men were omitted from the analysis. The study also did not report data on the calcium intake within the tertiles. The methodological quality was C.

In the Japan CC study, 0.9 percent of women died of stroke. The study also found no consistent association between calcium intake and stroke death.

Findings per calcium intake level.

Among the outcomes for which studies had either statistically significant associations or suggestions of associations between calcium intake and cardiovascular events, the following findings of calcium intake level were reported.

Regarding the risk of overall cardiovascular mortality, one of two studies in women (Japan CC) found a suggestion that higher calcium intake may be associated with increased risk of cardiovascular death. The association can be seen for quintiles 2 to 4, where women in the lowest quintile had a median calcium intake of 266 mg/day and those in the second quintile had a median calcium intake of 379 mg/day.

Regarding the risk of cardiac mortality, one of three studies in women (Iowa WHS) found that women in the lowest quartile of calcium intake, below 696 mg/day, had the highest risk of cardiac mortality.

Regarding the risk of stroke, among studies of both sexes combined, two (Japan PHC and the Taiwanese CVD-FACTS) of three studies found a statistically significant association between lower calcium intake and higher risk of stroke. In Japan PHC, those in the third to fifth quintiles, with median calcium intakes of 439 mg/day or higher, had lower risks than those in the lowest quintile. Those in the second quintile had a median calcium intake of 344 mg/day and those in the lowest quintile 233 mg/day. In CVD-FACTS, those in the two tertiles with calcium intake below 591 mg/day had about a 50 percent increased risk of stroke compared to those with higher calcium intake. The two studies restricted to men had opposite findings. The HPFS found lower risks of stroke among men in the third to fifth quintiles of calcium intake (median 800 mg/day or higher) compared to the lowest quintile (median 500 mg/day). Those in the second quintile had a median calcium intake of 700 mg/day. In contrast, the ATBC study in Finland found somewhat higher risks of stroke (RR~1.1) in all quintiles above the lowest quintile. The median calcium intakes in the first and second quintiles were 876 and 1178 mg/day, respectively. The one study of women (NHS) had lower risks of stroke in all quintiles above the lowest quintile. The median calcium intakes in the first and second quintiles were 395 and 645 mg/day, respectively.

Findings per age and sex.

The majority of studies (and the large majority of individuals) included mostly people between the ages of about 40 and 70 years. The youngest individuals included were 32 year old women in the NHS. Apparently very few individuals were over the age of 70 years. Only a small Finnish study (Marniemi 2005[48]) restricted the study cohort to only older adults (65 years and older). This study found no significant associations between calcium intake and cardiovascular events. No study reported a subgroup analysis based on age. The reported data do not allow further conclusions based on age.

Almost all studies or analyses separately evaluated men and women. The findings that could be interpreted as an association between calcium intake and cardiovascular risk were mostly found in women (low calcium intake being associated with increased risk of cardiac death (in one of three studies) and stroke (in a single study), but with lowered risk of overall cardiovascular death (in one of two studies). The only potential associations between calcium intake and cardiovascular events in men were found for stroke; however, the two studies had opposite findings about the direction of the association.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed

- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** Overall, the studies included relatively few people in this life stage. All were at least 32 years old, and most were at least 40 to 45 years old. However, the one study of stroke in women was conducted in women who were mostly in this life stage. Those in the lowest quintile of the NHS appear to have had higher risks of stroke than those women with greater calcium intake.
- **51 – 70 y** The majority of evidence regards people in this life stage. Overall, the majority of analyses found no significant association between calcium intake and most cardiovascular events. Only for stroke did at least two studies find significant associations between calcium intake and the outcome. In two Asian studies, where the average dietary calcium intake was about half that in the US and which also included people in the younger life stage, stroke risk was progressively higher in lower quantiles (maximum quantiles were median of 753 mg/day and >591 mg/day). For studies of people within this life stage, other significant associations were found in one of three studies of cardiac death in women (calcium intake below 696 mg/day was associated with increased risk) and in one of two studies of cardiovascular death in women (calcium intake above about 300 mg/day may be associated with increased risk).
- **≥71 y** Few studies included people in this life stage. The one study of people in this life stage found no association between calcium intake and cardiac events or stroke in a relatively small, quality C study.
- **Postmenopause** Only the Iowa WHS included primarily postmenopausal women. In their analysis, calcium intake below 696 mg/day was associated with increased risk of ischemic heart disease death.
- **Pregnant & lactating women** Not reviewed

Table 49. Calcium and cardiovascular outcomes: Characteristics of cohort studies[B]

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Al-Delaimy 2003[107] HPFS US (various) [12663277]	• Health status • Mean age (SD), y • Male (%)	No CVD 54 (9) 100	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Outcome stratified by total Ca intake quintiles	X	X	X	X		X	IHD MI Cardiac death Total Ca (both)
Ascherio 1998[109] HPFS US (various) [9743511]	• Health status • Mean age (range), y • Male (%)	No CVD nd (40-75) 100	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Outcome stratified by total Ca intake quintiles	X	X	X	X		X	Stroke Total Ca (both)
Bostick 1999[110] Iowa WHS Iowa (42°) [9921960]	• Health status • Mean age (range), y • Male (%)	No IHD 61 (55-69) 0	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Outcome stratified by total Ca intake quartiles	X	X	X	X		X	Cardiac death Total Ca (both)
Iso 1999[111] NHS US (various) [10471422]	• Health status • Mean age (range), y • Male (%)	No CVD 46 (32-57) 0	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles		X				X	Stroke Total Ca (food)
Larsson 2008[112] ATBC SW Finland (~60°N) [18332289]	• Health status • Mean age (range), y • Male (%)	No stroke 57 (50-69) 100	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles	X	X	X	X		X	Stroke (cerebral infarct) Total Ca (food)
Marniemi 2005[48] Turku Finland (60°N) [15955467]	• Health status • Mean age (range), y • Male (%)	Any 79 (65-99) 48%	• Dietary assessment method • Internal validation? (y/n)	Interview No	Outcome stratified by total Ca intake tertiles	X	X				X	MI Stroke Total Ca (both)

continued

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Ross 1997[113A] Shanghai China (31°N) [9236416]	• Health status • Mean age (range), y • Male (%)	Cases & controls nd (45-64) 100	• Dietary assessment method • Internal validation? (y/n)	FFQ nd	Outcome stratified by total Ca intake tertiles		X	X	X		X	Fatal stroke Total Ca (food)
Umesawa 2006[104] Japan CC Japan (various) [16339476]	• Health status • Mean age (range), y • Male (%)	No CVD 56 (40-79) 39	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles	X	X	X	X		X	Cardiac death Stroke death CVD death Total Ca (food)
Umesawa 2008[106] Japan PHC Japan (various) [18635855]	• Health status • Mean age (range), y • Male (%)	No CVD 49 (40-59) 48	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Outcome stratified by total Ca intake quintiles	X	X	X	X		X	CHD Stroke Total Ca (food)
van der Vijver 1992[105] Dutch civil servants Amsterdam Netherlands (52°) [1544755]	• Health status • Mean age (range), y • Male (%)	Any 52 (40-65) 51	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles		X	X			X	Cardiac death CVD death Total Ca (food)
Weng 2008[108] CVD—FACTS Taiwan (22°-25°) [18988909]	• Health status • Mean age (range), y • Male (%)	No stroke, cancer 57 (≥40) 44	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quartiles (top 2 quartiles combined)		X	X	X		X	Ischemic stroke Total Ca (both)

[A] Nested case-control study
[B] This table is ordered alphabetically by study author

Table 50. Calcium and cardiovascular outcomes: Results of cohort studies

Author Year Study Name PMID	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
CVD Death										
Men										
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Men	CVD death (685/23,117; 0.030)	8.9 y	250, mean	140	4623	**1**	**Reference**	0.95	B
				363	141	4624	0.98	0.75, 1.30		
				449	135	4623	0.93	0.67, 1.29		
				536	135	4624	0.92	0.64, 1.32		
				665	134	4623	0.97	0.64, 1.48		
van der Vijver 1992[105] Dutch civil servants [1544755]	40-65 y, Men	CVD death (nd/1340; ~0.27, age-adjusted)	28 y	≤585	31.9%, age-adjusted	271	1.3	0.8, 1.9	nd	B
				585-1245	26.7%	798	1.1	0.8, 1.5		
				>1245	24.9%	271	**1**	**Reference**		
Women										
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Women	CVD death (644/35,609; 0.018)	8.9 y	266, mean	153	7121	**1**	**Reference**	0.14	B
				379	156	7122	1.29	0.99, 1.67		
				462	136	7122	1.24	0.90, 1.69		
				545	98	7122	0.92	0.64, 1.34		
				667	101	7122	1.14	0.74, 1.74		
van der Vijver 1992[105] Dutch civil servants [1544755]	40-65 y, Women	CVD death (nd/1265; ~0.14, age-adjusted)	28 y	≤445	14.6%, age-adjusted	258	1.1	0.6, 2.0	nd	B
				445-850	14.4%	750	1.1	0.7, 1.7		
				>850	12.6%	257	**1**	**Reference**		
Cardiac Events, Total										
Both Sexes										
Umesawa 2008[106] Japan PHC [18635855]	40-59 y, Both	CHD (322/41,526; 0.0078)	13 y	233, median	72	~8305	**1**	**Reference**	NS	A
				344	72	~8305	1.18	0.83, 1.68		
				439	56	~8305	0.91	0.60, 1.37		
				603	58	~8305	1.08	0.71, 1.65		
				753	64	~8305	0.93	0.58, 1.50		

continued

Author Year Study Name PMID	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Marniemi 2005[48] (Finland) [15955467]	65-99 y, Both	AMI (130/755; 0.172)	10 y	nd	nd	~252	**1**	**Reference**	nd	C
				nd	nd	~252	0.87	0.57, 1.37		
				nd	nd	~252	1.14	0.70, 1.84		
Men										
Al-Delaimy 2003[107] HPFS [12663277]	Mean (SD) 54 (9) y, Men	IHD, total (1458/39,800; 0.037)	12 y	523, mean	300	7960	**1**	**Reference**	0.43	A
				670	296	7960	1.03	0.88, 1.22		
				803	267	7960	0.92	0.78, 1.09		
				995	299	7960	1.01	0.85, 1.19		
				1377	296	7960	0.94	0.79, 1.11		
Cardiac Death Men										
Al-Delaimy 2003[107] HPFS [12663277]	Mean (SD) 54 (9) y, Men	IHD death (428/39,800; 0.011)	12 y	523, mean	88	7960	**1**	**Reference**	0.72	A
				670	90	7960	1.17	0.87, 1.50		
				803	70	7960	0.93	0.67, 1.29		
				995	79	7960	1.06	0.77, 1.47		
				1377	101	7960	1.10	0.79, 1.51		
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Men	CHD death (148/23,117; 0.0064)	8.9 y	250, mean	37	4623	**1**	**Reference**	0.43	A
				363	26	4624	0.84	0.47, 1.50		
				449	33	4623	1.20	0.62, 2.30		
				536	32	4624	1.27	0.60, 2.68		
				665	20	4623	0.92	0.37, 2.29		
van der Vijver 1992[105] Dutch civil servants 1544755	40-65 y, Men	CHD death (nd/1340; ~0.15, age-adjusted)	28 y	≤585	16.6%, age-adjusted	271	0.9	0.6, 1.6	nd	B
				585-1245	15.1%	798	1.0	0.6, 1.5		
				>1245	14.5%	271	**1**	**Reference**		
Women										
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Women	CHD death (116/35,609; 0.0033)	8.9 y	266, mean	38	7121	**1**	**Reference**	0.50	A
				379	21	7122	0.88	0.48, 1.62		
				462	25	7122	1.28	0.62, 2.61		
				545	17	7122	0.84	0.35, 2.02		
				667	15	7122	0.87	0.31, 2.45		

continued

Author Year Study Name PMID	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Bostick 1999[110] Iowa WHS [9921960]	55-69 y, Women	IHD death (387/34,486; 0.011)	8 y	<696	127	~8621	**1**	**Reference**	0.09	B
				696-1051	84	~8621	0.62	0.45, 0.85*		
				1052-1425	94	~8621	0.75	0.55, 1.03		
				>1425	82	~8621	0.67	0.47, 0.94*		
van der Vijver 1992[105] Dutch civil servants [1544755]	40-65 y, Women	CHD death (nd/1265; ~0.06, age-adjusted)	28 y	≤445	6.2%, age-adjusted	258	1.1	0.5, 2.5	nd	B
				445-850	6.3%	750	1.2	0.6, 2.3		
				>850	4.4%	257	**1**	**Reference**		
Cardiac Event, Nonfatal										
Men										
Al-Delaimy 2003[107] HPFS [12663277]	Mean (SD) 54 (9) y, Men	Nonfatal MI (1030/39,800; 0.026)	12 y	523, mean	212	7960	**1**	**Reference**	0.43	A
				670	206	7960	1.01	0.83, 1.23		
				803	197	7960	0.96	0.78, 1.17		
				995	220	7960	1.04	0.85, 1.28		
				1377	195	7960	0.92	0.74, 1.14		
Stroke										
Both Sexes										
Umesawa 2008[106] Japan PHC [18635855]	40-59 y, Both	Stroke, Total (1321/41,526; 0.032)	13 y	233, median	314	~8305	**1**	**Reference**	0.02	A
				344	257	~8305	0.94	0.79, 1.13		
				439	252	~8305	0.79	0.65, 0.97*		
				603	247	~8305	0.78	0.63, 0.96*		
				753	251	~8305	0.71	0.56, 0.89*		
Weng 2008[108] CVD—FACTS [18988909]	≥40 y Both	Stroke, Ischemic (132/1772; 0.074)	10.6 y	<451	nd	443	1.52	0.98, 2.35	0.03	B
				451-591	nd	443	1.49	0.99, 2.24		
				>591	nd	886	**1**	**Reference**		
Marniemi 2005[48] (Finland) [15955467]	65-99 y, Both	Stroke, Total (70/755; 0.093)	10 y	nd	nd	~252	**1**	**Reference**	nd	C
				nd	nd	~252	0.981	0.53, 1.81		
				nd	nd	~252	1.34	0.70, 2.55		
Men										

continued

Author Year Study Name PMID	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Ascherio 1998[109] HPFS [9743511]	40-75 y, Men	Stroke, Total (328/43,738; 0.0075)	8 y	500, median	75	~8748	**1**	**Reference**	0.10	A
				700	69	~8748	0.95	0.68, 1.32		
				800	51	~8748	0.72	0.50, 1.03		
				1000	63	~8748	0.84	0.60, 1.19		
				1400	70	~8748	0.88	0.63, 1.23		
Larsson 2008[112] ATBC [18332289]	50-69 y, Men	Cerebral infarction (2702/26,556; 0.102)	13.6 y	876, median	518	~5311	**1**	**Reference**	0.09	C
				1178	541	~5311	1.08	0.95, 1.22		
				1379	542	~5311	1.09	0.96, 1.23		
				1581	546	~5311	1.11	0.98, 1.26		
				1916	555	~5311	1.10	0.98, 1.26		
Women										
Iso 1999[111] NHS [10471422]	32-57 y, Women	Stroke, Total (690/85,764; 0.0080)	14 y	395, median	165	~17153	**1**	**Reference**	NS	A
				645	132	~17153	0.79	0.63, 1.00*		
				675	117	~17153	0.71	0.56, 0.90*		
				837	142	~17153	0.87	0.70, 1.09		
				1145	134	~17153	0.83	0.66, 1.04		
Stroke, Fatal										
Men										
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Men	Stroke death (322/23,117; 0.014)	8.9 y	250, mean	61	4623	**1**	**Reference**	0.95	A
				363	76	4624	1.14	0.76, 1.70		
				449	69	4623	0.90	0.56, 1.45		
				536	59	4624	0.69	0.40, 1.18		
				665	57	4623	0.68	0.37, 1.26		
Ross 1997[113A] (China) [9236416]	45-64 y, Men	Stroke death (245/18,244;0.013) [245 cases vs. 1225 controls]	12 y	nd	103	460 controls	**1**	**Reference**	NS	C
				nd	68	369 controls	0.8	0.6, 1.6		
				nd	74	396 controls	1.0	0.8, 1.4		
Women										
Umesawa 2006[104] Japan CC [16339476]	40-79 y, Women	Stroke death (322/35,609; 0.0090)	8.9 y	266, mean	70	7121	**1**	**Reference**	0.50	A
				379	82	7122	1.38	0.95, 2.01		
				462	73	7122	1.24	0.79, 1.95		
				545	42	7122	0.69	0.40, 1.18		
				667	55	7122	0.94	0.51, 1.72		

* Statistically significant (P<0.05)
[A] Case-control study from prospective, longitudinal cohort.

Figure 11. Cardiovascular outcomes risk stratified by calcium intake

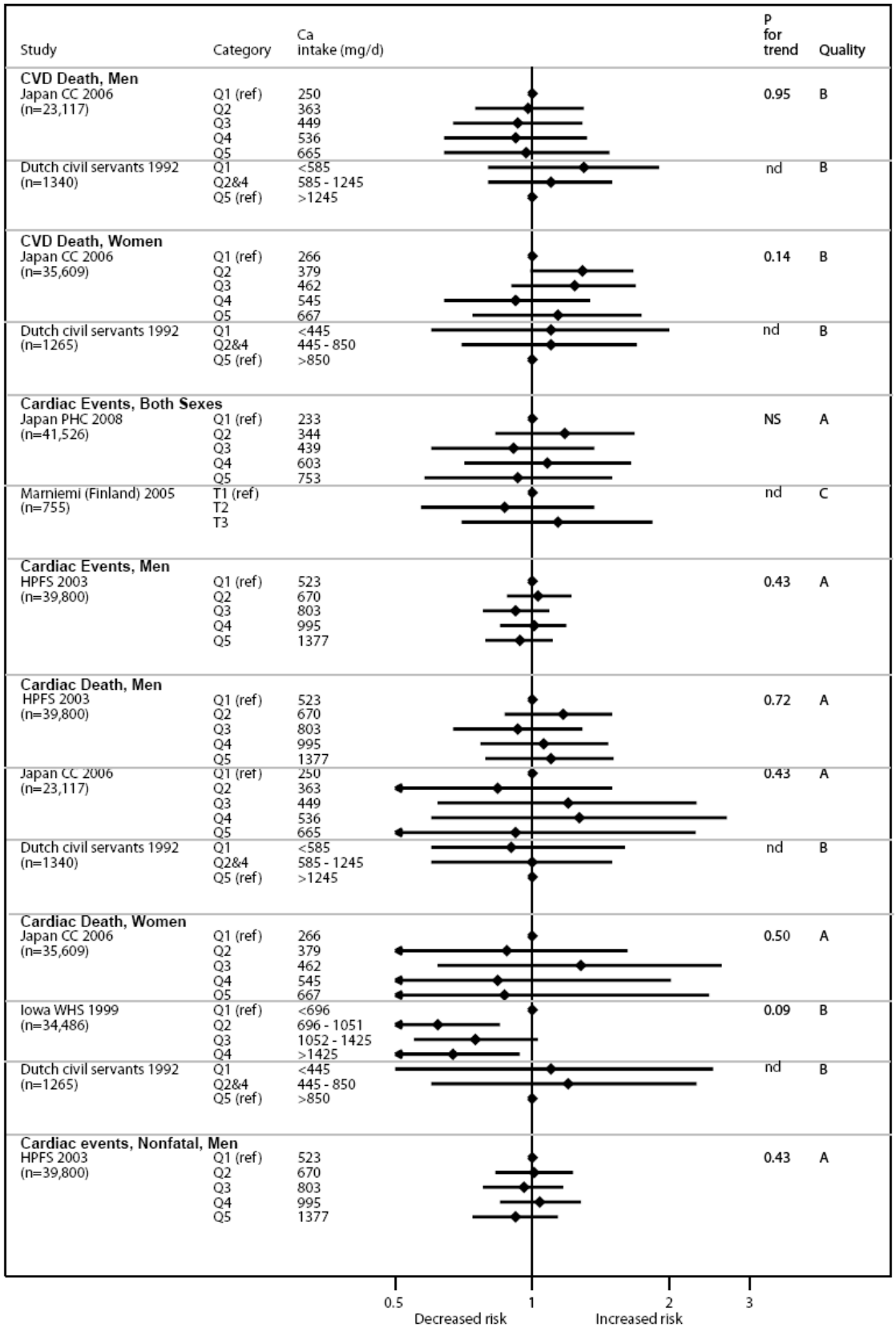
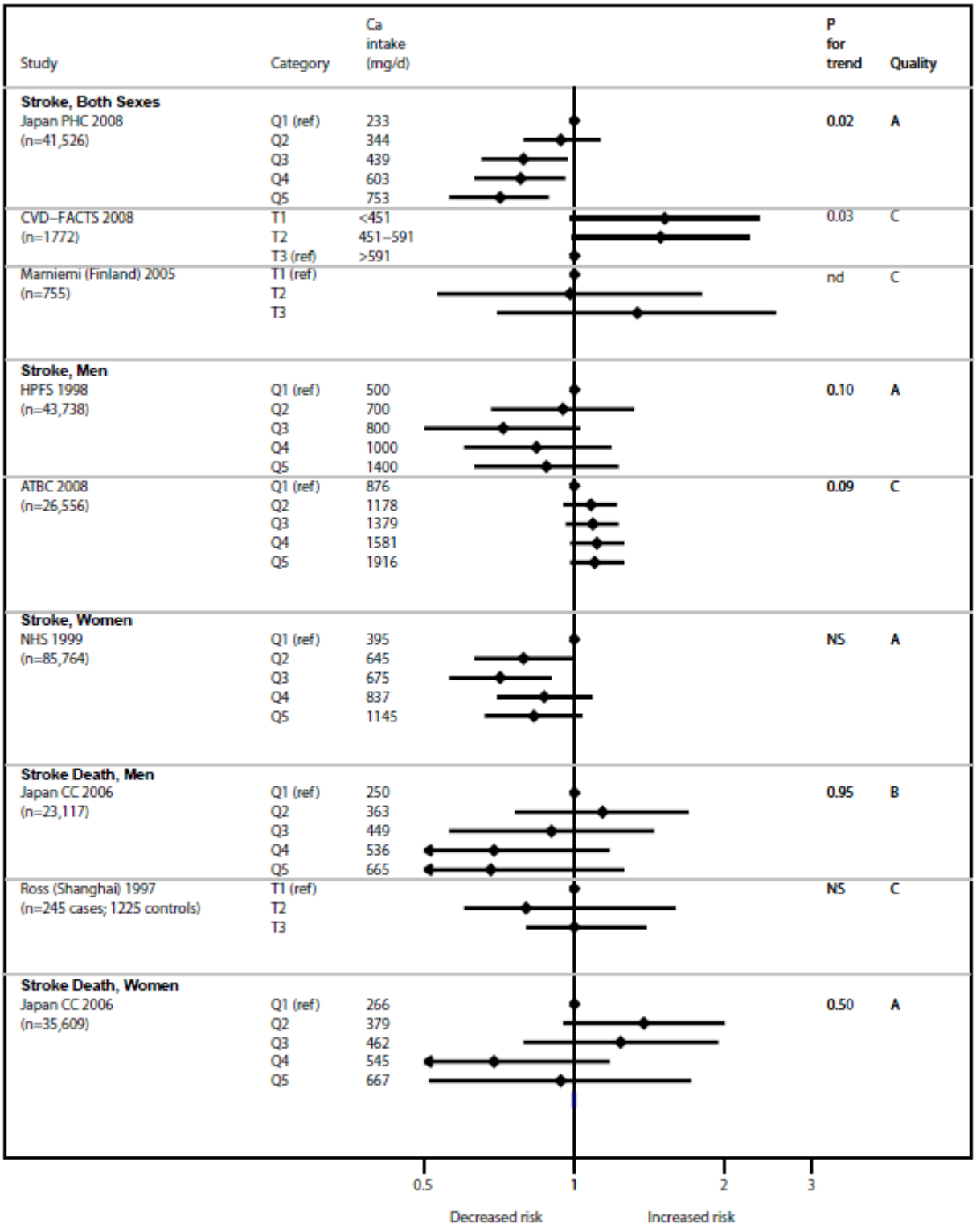


Figure 12. Stroke risk stratified by calcium intake



Calcium and Body Weight

We searched for systematic reviews and primary studies that evaluated associations between calcium intake or body stores and *incidence of overweight or obesity*; no such studies were found. For the outcome *weight change* (in kilograms or body mass index units), we included only randomized controlled trials. The EPC and the TEP agreed that the limited resources would not be expended on reviewing observational studies for the surrogate outcome body weight (where overweight or obesity are considered to be the clinical outcomes). We included only studies of adults. Studies of weight gain in children are included in the "Growth" section.

Synopsis.

No studies evaluated the association of calcium intake and incidence of overweight or obesity. We identified three systematic reviews that evaluated RCTs of calcium intake and changes in body weight. Eight additional trials not identified by these systematic reviews met eligibility criteria for this report and are summarized together with the systematic reviews. Altogether, 49 trials have been identified by the previous and current systematic reviews. Because the systematic reviews all used somewhat different eligibility criteria, they included overlapping groups of trials. No one or two systematic reviews captured most of the relevant trials; therefore, all systematic reviews are included here.

The three systematic reviews performed separate analyses for calcium supplementation and dairy product intake. Only one of the systematic reviews separately analyzed studies of people on isocaloric diets (where weight loss was not a goal) and studies of people on energy-restricted diets. Overall, 24 included trials investigated calcium supplementation and 15 investigated dairy product intake; 29 trials had isocaloric background diets and 13 evaluated calcium supplementation in the setting of an energy-restricted (weight loss) diets. Although there was not complete agreement among the systematic reviews, overall, the trials in the systematic review do not support an effect of calcium (or dairy) supplementation on body weight. No systematic review analyzed effects of calcium supplementation based on life stage or calcium dose.

Seven of the eight additional trials investigated calcium supplements in the setting of isocaloric diets; two of the trials investigated calcium supplements in overweight people on energy-restricted diets. All these trials found no significant effect of calcium supplementation on body weight.

Detailed presentation (Tables 51, 52, & 53).

The three systematic reviews explicitly or implicitly used generally different eligibility criteria, resulting in large overlaps in the trials included among the reports.[114-116]. Overall, the systematic reviews included 42 trials. All systematic reviews separately analyzed calcium supplementation and dairy product intake. The largest, most recent systematic review[114] included trials up to 2007, separated isocaloric from energy-restricted trials, but did not perform meta-analysis. The next largest systematic review[115] included trials through 2004. The last systematic review,[116] through 2001, also did not perform meta-analyses. All the dairy product trials in this review were also included in the most recent systematic review and are thus not discussed further here. Seven more recent calcium supplementation trials not included in any of the systematic reviews were found.[117-123]

Isocaloric trials.

The systematic review by Lanou et al. (2008)[114] evaluated 19 isocaloric trials of increased calcium intake in adults. Nine trials compared calcium supplements to placebo; 10 trials compared high calcium dairy intake to lower calcium nondairy intake. The systematic review did not provide details of every included trial, nor was meta-analysis performed. In summary, 16 trials (8 calcium supplement, 8 dairy product) of the 19 trials reported no significant effect of increased calcium intake on body weight, 1 calcium trial found significantly greater weight loss in those receiving calcium supplements, and 2 dairy trials found significantly greater weight *gain* in those in the dairy product group. This latter finding was theorized to be due to the extra calories from the dairy products.

Seven additional isocaloric trials were not included in the systematic reviews.[117-122,124] Four of these trials were conducted in postmenopausal women, two in young women (age early 20s), and one in men and women aged 30 to 34 years. The trials used a variety of calcium compounds with doses ranging from 800 to 2000 mg; one compared dairy (~1250 mg calcium) to nondairy (~375 mg calcium) intakes.[120] The studies ranged in duration from 1 month to almost 3 years. Among the studies, one was of methodological quality A, three B, and three C. Methodological limitations included inadequate reporting of methodology or outcomes, statistical issues, high dropout rates, and large difference in baseline weights between groups. The participants' weights were generally stable, on average changing less than 1 kg during 6 weeks to 3 years of followup. The net weight changes (calcium group minus control group) ranged from -0.8 to +0.5 kg. No trial found a significant effect of calcium.

Findings per calcium intake level.

Overall, there was no evidence of different effects related to calcium intake level. No study directly compared a range of calcium intake levels.

Findings per age and sex

The systematic review did not address the question of different effects based on age or sex. Among the additional trials reviewed here, no significant difference was found across trials of different populations. Most were conducted in postmenopausal women.

Energy-restricted diets.

The systematic review by Lanou et al. (2008)[114] evaluated 11 trials that compared dairy intake (6 trials) or calcium supplements (5 trials) in the setting of energy-restricted diets with the goal of weight loss. Of the six dairy product trials, three were conducted by the same investigators. These three trials all reported significantly more weight loss in participants with high dairy product intake than those with low or no dairy product intake (1137 vs. 430 mg Ca; 1100 vs. 500 mg; 3 vs. <1 servings). The systematic review authors note that due to incomplete reporting in the trials, it was impossible to determine whether the difference in weight loss may have been due to differences in calcium (or dairy) intake or differential compliance with the calorie restriction protocol. One of the five calcium supplement trials, which was part of one of the positive dairy trials by the same researchers, found greater weight loss with calcium supplementation; the others found no significant effect.

The two additional trials not included in the systematic reviews reported no significant effects of calcium supplementation on body weight loss.[119,123] Both trials were conducted in overweight women, one trial with a mean age of 49 years and one trial of postmenopausal women. One trial compared two different formulations of 500 mg calcium with placebo in the

setting of a low calcium intake (350 mg/day); the other compared higher (1200 mg) to lower (400 mg) doses of calcium citrate. Over 3 or 6 weeks, women in all trial groups lost between 3.3 and 4.3 kg, with no significant differences between those with higher than lower calcium intake.

Findings per calcium intake level.

Overall, there was no evidence of different effects related to calcium intake level. No study directly compared a range of calcium intake levels.

Findings per age and sex.

The systematic review did not address the question of different effects based on age or sex. The two additional trials did not add any information regarding age or sex subgroups.

Combined isocaloric and energy-restricted diets.

Two of the systematic reviews did not separately analyze studies based on background diet (regarding weight). The systematic review by Trowman et al. (2006)[115] performed meta-analyses of 13 trials, separately for calcium supplement and dairy product trials. This systematic review found a significant effect of calcium supplements (weighted mean difference = -1.79 [95 percent CI -3.04, -0.55]) suggesting greater weight loss (or smaller weight gain) in adults taking calcium supplements. However, the investigators noted that the difference in effect of calcium supplement trials may be due to significant differences (in aggregate) in the baseline weights of the two arms. Across studies, the calcium supplement group participants had significantly lower body weights at baseline. The meta-analysis of dairy trials found no significant effect of dairy products on body weight. The systematic review by Barr et al. (2003)[116] reviewed both calcium supplement and dairy trials; however, the dairy trials were all included in the later systematic review by Lanou et al. (2008)[114] and are thus not repeated here. Among the eight trials of calcium supplementation, all but one found no significant effect on body weight. Between the two systematic reviews, over two-thirds of the trials were conducted in post- or perimenopausal women; the mean age of participants (among trials with data reported in the systematic reviews) ranged from 36 to 72 years. Only four of the trials were conducted in men. The range of calcium supplement doses was 700 to 1600 mg/day, with most studies using 1000 mg. The range of calcium intake among the dairy trials was 610 to 2400 mg/day. In the Trowman et al. (2006) systematic review,[115] the range of followup durations of the trials was 12 weeks to 3 years. The Barr et al. (2003) systematic review[116] included longer duration trials, ranging from 6 months to 4 years.

Findings per calcium intake level.

The systematic reviews did not find evidence of differential effects based on calcium intake level (supplement dose or dairy calcium).

Findings per age and sex.

The large majority of trials reviewed in the systematic reviews were conducted in postmenopausal women. The systematic reviews did not find evidence of differential effects based on age or sex.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed

- **19 – 50 y** Many of the trials are applicable to people within this life stage; though relatively few trials included men. For both people on energy-restrictive diets and on isocaloric diets, overall, the evidence suggests no significant effect on body weight with increased calcium intake, either as supplements or from dairy product intake.
- **51 – 70 y** The majority of studies are applicable to women within this life stage; few trials included men. The conclusions are the same as for those in the 19-50 y life stage.
- **≥71 y** The evidence is scant for this life stage. Few of the studies appear to have included people over age 70 years.
- **Postmenopause** The majority of studies are applicable to postmenopausal women. The conclusions are the same as for those in the 19-50 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 51. Systematic reviews of calcium supplementation and weight

Author Year [PMID]	Lanou 2008[114] [18454813]
Design (Search Years)	Randomized controlled trials (1966-2007)
Population	All, generally healthy (adults and children, only studies of adults included here)
Intervention and Comparator	Calcium supplements or dairy intake versus no supplement or low calcium intake
Results	29 trials[A] No energy restriction Calcium supplement: 8/9 trials no significant effect. 1 found significantly more weight loss on calcium supplement. Dairy supplementation: 8/10 trials no significant effect. 2 found significantly more weight gain among those on dairy Energy restriction Calcium supplement: 4/5 trials no significant effect. 1 found significantly more weight loss with calcium. Dairy supplementation: 3/6 trials significantly more weight loss on high calcium intake All 4 trials with significant differences were by same study investigators
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	None
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?		Only published trials. Excluded studies not enumerated or listed.	

Author Year [PMID]	Trowman 2006[115] [16768823]
Design (Search Years)	Randomized controlled trials (1800[B]/2002-2004)
Population	Nonpregnant, nonlactating, ≥18 y
Intervention and Comparator	Calcium supplements or dairy intake versus no supplement or low calcium intake
Results	13 trials Calcium supplement WMD = -1.79 (-3.04, -0.55)[C], statistically homogeneous Dairy supplementation WMD = +0.85 (-4.39, +6.08), statistically heterogeneous ANCOVA, adjusting for baseline weight: Calcium Effect = -0.41 (-1.07, +0.25) kg Dairy Effect = +0.23 (-2.88, +3.34) kg
Comments	Apparent difference in effect of calcium supplement trials may be due to significant differences (in aggregate) in baseline weights of two arms across studies (intervention arm participants were significantly lighter at baseline).

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Debatable
All publication types and languages included?	Yes (implied)	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Used WMD instead of net difference, then needed to perform an ANCOVA to adjust for baseline differences.	

continued

Author Year [PMID]	Barr 2003[116] [12514301]
Design (Search Years)	Randomized controlled trials (1966-2001)
Population	All, generally healthy (adults and children, only studies of adults included here)
Intervention and Comparator	Calcium supplement or dietary calcium versus no supplement or usual calcium intake (see Comment)
Results	8 trials Calcium supplement 7/8 trials found no significant effect
Comments	6 dairy supplementation trials reviewed. Not included here. These represent a subset of the dairy trials reviewed by Lanou 2008[114]

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	None
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Studies published in English only. Excluded studies not enumerated or listed.	

WMD, weighted mean difference

[A] The systematic review included the Women's Health Initiative (WHI) trial of vitamin D + calcium supplementation. This trial is omitted here and is discussed separately in the vitamin D + calcium and body weight section.

[B] Cochrane Library Database of Controlled Trials

[C] Numbers in parentheses are 95% confidence intervals

Table 52. Calcium and weight: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Yamamoto 1995[117] TOHP US (various) [7795837]	• Health status • Mean age (range), y • Male (%)	Healthy 43 (30-54) 69	Ca 970 mg/d	Ca carbonate vs placebo	Eligibility for randomization required consumption of at least two-thirds of 6 wks of supplement placebo dosing. During the study, pill counts averaged 95% (with three-fourths taking at least 95% of their supplements).	
van Beresteyn 1986[118] Netherlands (52°N) [3788835]	• Health status • Mean age (range/SD), y • Male (%)	Healthy 21 (20-23) 0	nd	Ca carbonate vs placebo	nd	
Cifuentes 2004[119] New Brunswick, NJ (40°N) [15213038]	• Health status • Mean age (range), y • Male (%)	Overweight, post-menopause 61 (52-75) 0	nd	Ca supplement vs placebo	nd	Factorial design with weight loss and maintenance diets
Ghadirian 1995[120] Montreal, Canada (46°N) [7493659]	• Health status • Mean age (range), y • Male (%)	Healthy, post-menopause ~80 (~≥50) 0	Ca 776 mg/d	Dairy vs dairy free intake	Non-compliant and those who provided incomplete data were excluded.	
Aloia 1995[121] Mineola, NY (41°N) [7892882]	• Health status • Mean age (SD), y • Male (%)	Healthy, post-menopause 53 (0.6) 0	nd	Ca supplement vs placebo (Vit D in both groups)	nd	
Thomsen 1987[122] Copenhagen, Denmark (55°N) [3307307]	• Health status • Mean age (range/SD), y • Male (%)	Healthy, post-menopause nd 0	nd	Combination Ca lactate-gluconate & Ca carbonate vs placebo	nd	
Bortolotti 2008[124] Lausanne, Switzerland (47°N) [18842771]	• Health status • Mean age (SE), y • Male (%)	Healthy 22 (1.2) 30	Ca 586 (137 SE) mg/d, all <800 mg/d	Ca phosphate vs placebo	Measured but not reported	Crossover study (5 wk with 10 wk washout), 1° outcomes were metabolic
Kabrnova-Hlavata 2008[123] Lausanne, Czech Rep (50°N) [17552880]	• Health status • Mean age (SD), y • Male (%) • Male (%)	Overweight, healthy 49 (12) 0 0	nd	Ca carbonate vs “lactoval” vs placebo	nd (a dietitian checked that subjects took tablets)	Energy restriction

Table 53. Calcium and weight: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Isocaloric														
Yamamoto 1995[117] TOHP [7795837]	30-54 y, Both	BMI	2°	6 mo	Ca carbonate 1000 mg	217	Kg/m^2	27.4	+0.07	-0.05, 0.19	-0.05[A]	-0.23, 0.13[B]	NS	A
					Placebo	218		27.0	+0.12	-0.02, 0.26				
van Beresteyn 1986[118] Netherlands [3788835]	20-23 y, Women	Weight	2°	6 wk	Ca carbonate 1500 mg	29	Kg	61.8	-0.3	-2.7, 2.1[B]	-0.8	-4.3, 2.7[B]	NS	B
					Placebo	29		62.5	+0.5	-2.0, 3.0[B]				
		BMI	2°		Ca	29	Kg/m^2	20.8	-0.1	-0.8, 0.6[B]	-0.2	-1.2, 0.8[B]	NS	
					Placebo	29		21.0	+0.1	-0.6, 0.8[B]				
Cifuentes 2004[119] New Jersey [15213038]	52-75 y, Women	Weight	1°	6 wk	Ca citrate 1200 mg	10	Kg	70.9	0	-3.3, 3.3[B]	-0.4[C]	-5.5, 4.7[B]	NS	B
					Ca citrate 400 mg	15		68.0	+0.4	-3.4, 4.2[B]				
Ghadirian 1995[120] Canada [7493659]	~>=50 y, Women	Weight	2°	1 mo	Dairy intake (1242 mg Ca)	81	Kg	59.84	+0.10	-2.4, 2.6[B]	+0.5	-3.7, 4.7[B]	NS	C
					Nondairy intake (377 mg)	77		59.65	-0.40	-3.8, 3.0[B]				
Aloia 1995[121] New York [7892882]	Mean (SD) 53 (0.6) y, Women	Weight	2°	2.9 y	Ca 1700 mg[D] + Vit D 400 IU	36	Kg/y	65.8	+0.1	nd	0	nd	NS	C
					Vit D 400 IU	28		65.6	+0.1	nd				
Thomsen 1987[122] Denmark [3307307]	Early post-menopause, Women	Weight	2°	1 y	Ca lactate-gluconate & carbonate 2000 mg	14	Kg	60.6	+0.4	-2.4, 3.2[B]	-0.2	-8.0, 7.6[B]	NS	C
					Placebo	14		66.4	+0.6	-6.7, 7.9[B]				
Bortolotti 2008[124] Switzerland [18842771]	Mean (SE) 22 (1.2) y, Both	Weight	2°	5 wk	Ca phosphate 800 mg	10[E]	Kg	78.1	Final 80.0		Diff Final +0.4	-5.7, +6.5	NS	B
					Placebo				79.6					
Energy Restricted														

continued

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Kabrnova-Hlavata 2008[123] Czech Rep [17552880]	49 (SD) y, Women	Weight	2°	3 wk	Ca carbonate 500 mg + 350 mg Ca in diet (4.5 MJ/d)	21	Kg	85.37	-4.34	-4.9, -3.8	-0.47	-1.4, 0.4[B]	NS	B
					Lactoval (Ca phosphate, citrate, & lactate) 500 mg + 350 mg Ca in diet (4.5 MJ/d)	25		84.95	-3.34	-4.0, -2.6	+0.53	-0.5, 1.5[B]	NS	
					Placebo + 350 mg Ca in diet (4.5 MJ/d)	21		83.43	-3.87	-4.6, -3.2				
Cifuentes 2004[119] New Jersey [15213038]	52-75 y, Women	Weight	1°	6 wk	Ca citrate 1200 mg (>=2.5% wt loss goal)	16	Kg	71.5	-3.6	-6.4, -0.8[B]	-0.3[E]	-4.8, 4.2	NS	B
					Ca citrate 400 mg (>=2.5% wt loss goal)	16		74.5	-3.3	-6.8, 0.2[B]				

[A] Subgroup data available for black and white men and women (4 groups). No substantive differences among groups. All statistically nonsignificant.
[B] Estimated from reported data
[C] Adjusted for multiple factors, including baseline weight.
[D] No data on calcium type
[E] Crossover study
[F] Adjusted for multiple factors, including baseline weight

Calcium and Cancer

Cancer from all cause and total cancer mortality.

Synopsis.

No qualified systematic review evaluated associations between calcium intake and incidence of all cancer and total cancer mortality. One RCT showed a borderline nonsignificant reduction of the risk of total cancer among healthy postmenopausal women (>55 years old) living in Nebraska (latitude 41°N) who received calcium supplementation (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d). However, one cohort study analyzed US AARP cohort (men and women 50-71 y) showed that that total calcium intake was not associated with the risk of total cancer incident.

There is insufficient data to draw a conclusion regarding association between dietary calcium intakes and total cancer mortality.

Detailed presentation (Tables 54, 55, 56 & 57).

A 4-year population-based RCT,[52] sampled from a 9-county, largely rural area in eastern Nebraska (latitude 41°N), aimed to compare the efficacy of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) or calcium alone (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) to placebo in reducing fracture incidence. Incidence of cancer was a secondary outcome of this trial. A total of 743 postmenopausal women over 55 years old were analyzed for the effect of calcium supplementation alone. The mean serum 25(OH)D concentration at baseline was 72 nmol/L.

At the end of study the relative risk of developing cancer was 0.53 (95 percent CI 0.27, 1.03; P=0.06) comparing calcium supplementation (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) to the placebo. This study was rated B.

A cohort study analyzed data from AARP (the American Association of Retired Persons) members, aged 50 to 71 years old, living in six specific states in the US.[125] During 3,383,377 person-years of followup (over 7 years), a total of 36,965 cancer cases in men and 16,605 cancer cases in women were identified. The results showed that that total calcium intake was not associated with the risk of total cancer after controlling for potential risk factors pertinent to individual cancers. Methodological quality of this study was rated B.

Findings by age, sex and/or ethnicity.

A cohort study analyzing a total of 1553 men and 1397 women, aged between 40 and 65 years, living in Amsterdam (52°N) showed that there was no significant association between dietary calcium from foods and total cancer mortality in either men or in women after 28 years of followup.[126] This study was rated C because the food frequency questionnaire was not internally validated and could not estimate usual intake through 1-week food frequency recall.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data

- **19 – 50 y** A cohort study in Amsterdam included some men and women in this life stage. However, this study provided insufficient data regarding association between dietary calcium intakes and total cancer mortality.
- **51 – 70 y** The cohort study in Amsterdam also included some men and women in this life stage. However, this study provided insufficient data regarding association between dietary calcium intakes and total cancer mortality. One study analyzed US AARP cohort with men and women in this life stage showed that that total calcium intake was not associated with the risk of total cancer incident
- **≥71 y** No data
- **Postmenopause** One RCT with healthy postmenopausal women showed a borderline nonsignificant reduction of risk of total cancer by calcium supplementation (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d).
- **Pregnant & lactating women** No data

Table 54. Calcium and total cancer mortality: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2007[52] Nebraska, US 41º N [17556697]	• Health status • Mean age (range/SD), y • Male (%)	Mentally and physically fit 67 (7.3) 0	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo		

Table 55. Calcium and total cancer incidence or mortality: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Park 2009[125] NIH-AARP US 38º N [19237724]	• Health status • Mean age (range/), y • Male (%)	No cancer 50-71 60	• Dietary assessment method • Internal validation? (y/n)	FFQ (NCI-DHQ) USDA Nutrient Database y	Total cancer risk stratified by quintile of total calcium intake	X	X	X	X		X	Total calcium intake from diet and supplement
Slob 1993[126] Amsterdam 52° N [8478144]	• Health status • Mean age (range), y • Male (%)	nd 53 (40-65) 51	• Dietary assessment method • Internal validation? (y/n)	FFQ no	Cancer mortality stratified by dietary calcium intake quintiles (from foods only)	X	X					

Table 56. Calcium and total cancer mortality: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lappe 2007[52] nd [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Ca (citrate 1400 mg or carbonate 1500 mg)	17	445	RR Ca/placebo	0.53	0.27, 1.03	0.06	B
					Placebo	20	288					
	Post-menopausal women	Incident cancer (restrict to subjects who were free of cancer at 1 y intervention)	2°	4	Ca (citrate 1400 mg or carbonate 1500 mg)	15	416	RR Ca/placebo	0.59	0.29, 1.21	0.147	
					Placebo	18	266					

Table 57. Calcium and total cancer incidence or mortality: Results of cohort studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Park 2009 NIH-AARP[125] [19237724]	**50-71, males**	Total cancer (36,965/3,383,377 person-years)	7 y	526	36,965 (total)	3,383,377 person-years (total, both males and females)	**1 (HR)**	**Reference**	0.74	B
				498			0.99	0.96, 1.03		
				857			0.99	0.96, 1.03		
				1073			0.95[A]	0.96, 1.03		
				1530			0.99	0.95, 1.03		
	50-71, females	Total cancer (16,605/3,383,377 person-years)	7 y	494	16,605 (total)	3,383,377 person-years (total, both males and females)	**1 (HR)**	**Reference**	0.23	
				717			0.98	0.93, 1.03		
				969			0.94	0.89, 0.99*		
				1296			0.93	0.88, 0.98*		
				1881			0.96	0.91, 1.02		
Slob 1993[126] nd [8478144]	40-65 y, males	Cancer mortality (232/1553; 0.15)	28 y	≤585	nd	nd	1.0	0.6, 1.6	nd	C
				585 to ≤725	nd	nd	1.0	0.6, 1.6		
				725 to ≤935	nd	nd	1.0	0.6, 1.5		
				935 to ≤1245	nd	nd	0.8	0.5, 1.3		
				>1245	nd	nd	**1.0**	**Reference**		
	40-65 y, females	Cancer mortality (127/1397; 0.09)	28 y	≤445	nd	nd	1.1	0.6, 2.1	nd	
				445 to ≤540	nd	nd	0.8	0.4, 1.5		
				540 to ≤640	nd	nd	1.6	0.9, 2.8		
				640 to ≤850	nd	nd	1.4	0.7, 2.5		
				>850	nd	nd	**1.0**	**Reference**		

[A] Not a reasonable number based on the reported confidence interval; probably a typographical error in the article.

Prostate cancer.

We reviewed primary studies that evaluated associations between calcium intake and incidence and mortality of prostate cancer.

Synopsis.

No trials of calcium interventions evaluated prostate cancer. Four cohort studies rated A in methodological quality reported on the association between total calcium intake and the risk of prostate cancer. Three studies found significant associations between higher calcium intake and increased risk of prostate cancer. One study found the risk was higher in the group that took more than 1500 mg/d of calcium compared to those that took less than 700 mg/d (adjusted RR 1.3). A second study found only the group that took more than 2000 mg/d of calcium had higher risk of prostate cancer compared to those that took 500 to 749 mg/d of calcium (adjusted RR 1.26). A third study also found that male smokers who took more than 2000 mg/d of calcium had higher risk compared to those who took less than 1000 mg/d (adjusted RR 1.63). The fourth study found no relation between calcium intake (<500 to ≥2000 mg/d) and the risk of prostate cancer in men aged 50-70 years.

Detailed presentation (Tables 58 & 59; Figure 13).

A total of 12 cohort studies in 13 publications reported on the association between calcium intake and the risk of prostate cancer.[56,127-138] One of the studies also provided a post hoc analysis of an RCT on calcium supplement.[56] The incidence of prostate cancer in these studies ranged from 0.008 to 0.10. Most of the studies were conducted in Europe or North America, one study was conducted in Japan. Mean age of the subjects ranged from 53 to 67 years. Total calcium intake ranged from less than 500 mg/d to at least 2000 mg/d. Time between dietary assessment and the diagnosis of prostate cancer varied from 1 to 17 years. Methodological quality of four studies was rated A, seven studies were rated B, and one study was rated C.

19-50 years.

No study specifically targeted men between 19 to 50 years old.

51-70 years.

Twelve studies reported data on subjects with a mean age ranged from 53 to 67 years. Seven studies did not find an association between calcium intake and the risk of prostate cancer.[56,130,131,133,134,136,137] Five studies found that the risk was higher in the groups that took more calcium compared to the groups that took lower amount (adjusted OR 1.2-2.2).[127,129,132,135,138] The higher amount ranged from 921 to at least 2000 mg/d of calcium; the lower amount ranged from 455 to 1000 mg/d. Three studies also reported on the association between calcium intake and mortality from prostate cancer. Two studies found no association[130,134] and one study found an increased risk comparing the group that took at least 2000 mg/d of calcium with the group that took 500 to 749 mg/d (adjusted RR 2.02, 95 percent CI 1.14, 3.58).[129] One study was a post hoc analysis of an RCT of high calcium supplement (1200 mg/d) to prevent colorectal adenoma.[56] This study did not find an increased risk of prostate cancer in those supplemented with calcium compared to those who were not (unadjusted RR 0.83, 95 percent CI 0.52, 1.32). This study did not adjust for factors potentially relevant to prostate cancer.

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not reviewed
- **19 – 50 y** No study specifically targeted men 19 to 50 years old.
- **51 – 70 y** Seven studies did not find an association between calcium intake and the risk of prostate cancer. Five studies found that the risk was higher in the groups that took more calcium compared to the groups that took lower amount (adjusted OR 1.2-2.2). The higher amount ranged from 921 to at least 2000 mg/d; the lower amount ranged from 455 to 1000 mg/d.
- **≥71 y** No study specifically targeted men older than 70 years.
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Not applicable

Table 58. Calcium and prostate cancer: Characteristics of observational studies

Author, Year Trial/Cohort Name Country (Latitude) [PMID]	Population		Dietary calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
Park 2007[134] NIH-AARP Diet & Health US (multiple latitudes) [18000020]	Health status Mean age (range/SD), y Male (%)	12% current smoker 50-71(est.) 100	Dietary assessment method Internal validation? (y/n)	124-item FFQ y	Prostate cancer risk stratified by different intakes of calcium (dietary and supplement combined)	X	X	X	X		X	92% white; Total Ca (both)
Rodriguez 2003[135] CPS II Nutrition Cohort US (multiple latitudes) [12869397]	Health status Mean age (range/SD), y Male (%)	9.5% current smoker 64 100	Dietary assessment method Internal validation? (y/n)	68-item FFQ (modified Block) y	Prostate cancer risk stratified by different intakes of calcium (dietary and supplement combined & dietary calcium alone)	X	X	X			X	Total Ca (both)
Giovannucci 2006[128] 2007[129] HPFS US (multiple latitudes) [16492906] [17450530]	Health status Mean age (range/SD), y Male (%)	~10% current smoker 40-75 100	Dietary assessment method Internal validation? (y/n)	Semi-quantitative FFQ y	Prostate cancer risk stratified by different intakes of calcium (dietary and supplement combined)	X	X	X	X		X	>91% white; Total Ca (both)
Mitrou 2007[132] ATBC Finland (60°N) [17106437]	Health status Mean age (range/SD), y Male (%)	all smokers 57 (est.) 100	Dietary assessment method Internal validation? (y/n)	276-item FFQ y	Prostate cancer risk stratified by different intakes of calcium (dietary and supplement combined)	X	X	X	X		X	100% white; Total Ca (food)
Park 2007[133] MCS, HI, CA US (multiple latitudes) [17925283]	Health status Mean age (range/SD), y Male (%)	~17% current smoker 45-75 100	Dietary assessment method Internal validation? (y/n)	self-administered FFQ y	Prostate cancer risk stratified by different intakes of dietary calcium	X	X	X			X	~equal % of African Americans, native Hawaiians, Japanese Americans, Hispanics, whites; Total Ca (both)

continued

Author, Year Trial/Cohort Name Country (Latitude) [PMID]	Population		Dietary calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	Comments
Chan 2001[127] PHS US (multiple latitudes) [11566656]	Health status	on ASA, β-carotene, placebo trial; ~11% current smoker	Dietary assessment method	short self-administered questionnaire	Prostate cancer risk stratified by different intakes of dietary calcium		X	X			X	Total Ca (dairy)
	Mean age (range/SD), y	53										
	Male (%)	100	Internal validation? (y/n)	n								
Koh 2006[130] HAH US (multiple latitudes) [17106437]	Health status	7.5% smoker	Dietary assessment method	23-item FFQ (Willett 1985, 1987)	Prostate cancer risk stratified by different intakes of dietary calcium	X	X	X			X	Total Ca (dairy)
	Mean age (range/SD), y	67										
	Male (%)	100	Internal validation? (y/n)	n								
Schurrman 1999[137] Netherlands Cohort (52°N) [10362125]	Health status	nd	Dietary assessment method	150-item semi-quantitative FFQ	Prostate cancer risk stratified by quintile of dietary calcium intakes	X	X					Total Ca (food)
	Mean age (range/SD), y	61										
	Male (%)	100	Internal validation? (y/n)	n								
Kurahashi 2008[131] Japan PHC (multiple latitudes) [18398033]	Health status	~44% current smoker	Dietary assessment method	FFQ	Prostate cancer risk stratified by quartiles of dietary calcium intakes	X	X				X	Total Ca (food)
	Mean age (range/SD), y	45-74										
	Male (%)	100	Internal validation? (y/n)	y								
Rohrmann 2007[136] WCC, MD US (39ºN) [17315319]	Health status	17% current smoker	Dietary assessment method	60-item FFQ (Block)	Prostate cancer risk stratified by tertiles of calcium intakes (dietary and supplement combined)	X	X	X				99% white; Total Ca (both)
	Mean age (range/SD), y	54										
	Male (%)	100	Internal validation? (y/n)	n								

continued

Author, Year Trial/Cohort Name Country (Latitude) [PMID]	Population		Dietary calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
Tseng 2005[138] NHEFS US (multiple latitudes) [15883441]	Health status	nd	Dietary assessment method	105-item FFQ	Prostate cancer risk stratified by tertiles of calcium intakes (dietary and supplement combined)	X	X			X	X	88% white; 11% black; Total Ca (both)
	Mean age (range/SD), y	58(14.6)										
	Male (%)	100	Internal validation? (y/n)	n								
Baron 2005[56] CPP US (multiple latitudes) [15767334]	Health status	had >1 colon adenoma removal	Dietary assessment method	FFQ (Block, 1986)	Prostate cancer risk stratified by tertiles of dietary calcium intakes	X	X					5% black; Total Ca (suppl)
	Mean age (range/SD), y	62 (8.7)										
	Male (%)	100	Internal validation? (y/n)	N								

Table 59. Calcium and prostate cancer: Results of observational studies

Author Year Study Name [PMID]	Life Stage (male), y	Outcome (n/N; Incidence)	Followup Duration	Total Ca intake in mg/d	No. of Cases	Total no. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Park 2007[134] NIH-AARP Diet & Health [18000020]	51-70	Prostate cancer (10,180/293,888; 0.035)	8 y	<500	767	nd	1.01	0.93, 1.10	0.41	A
				500-<750	2927	nd	**1**	**Reference**		
				750-<1000	2808	nd	0.99	0.93, 1.04		
				1000-<1500	2572	nd	0.99	0.93, 1.05		
				1000-<1500	2572	nd	0.99	0.93, 1.05		
				≥2000	309	nd	0.97	0.85, 1.10		
		Mortality Prostate cancer		<500	11	nd	0.76	0.38, 1.53	0.99	
				500-<750	43	nd	**1**	**Reference**		
				750-<1000	56	nd	1.50	0.97, 2.32		
				1000-<1500	50	nd	1.42	0.86, 2.35		
				1500-<2000	18	nd	1.05	0.54, 2.05		
				≥2000	0	nd	-	-		
Rodriguez 2003[135] CPS II [12869397]	51-70	Prostate cancer (3811/65,321; 0.058)	≤7 y	<700	1323	23,653	**1**	**Reference**	0.02	A
				700-999	1293	nd	1.0	0.9, 1.1		
				1000-1499	835	nd	1.0	0.9, 1.1		
				1500-1999	265	nd	1.3	1.1, 1.5*		
				≥2000	95	1330	1.2	1.0, 1.6*		
Giovannucci 2006[128] 2007[129] HPFS [16492906] [17450530]	19-50 51-70	Prostate cancer (3544/47,750; 0.074)	≤16 y	<500	183	nd	0.98	0.84, 1.15	0.10	A
				750-999	1099	nd	1.07	0.98, 1.16		
				500-749	1072	nd	**1**	**Reference**		
				1500-1999	207	nd	1.06	0.91, 1.23		
				1000-1499	898	nd	1.03	0.94, 1.14		
				≥2000	85	nd	1.28	1.02, 1.60*		
		Mortality Prostate cancer		<500	21	nd	1.05	0.65, 1.69	0.01	
				750-999	81	nd	0.95	0.70, 1.28		
				500-749	94	nd	**1**	**Reference**		
				1500-1999	26	nd	1.56	1.0, 2.43*		
				1000-1499	76	nd	1.04	0.77, 1.42		
				≥2000	14	nd	2.02	1.14, 3.58*		

Continued

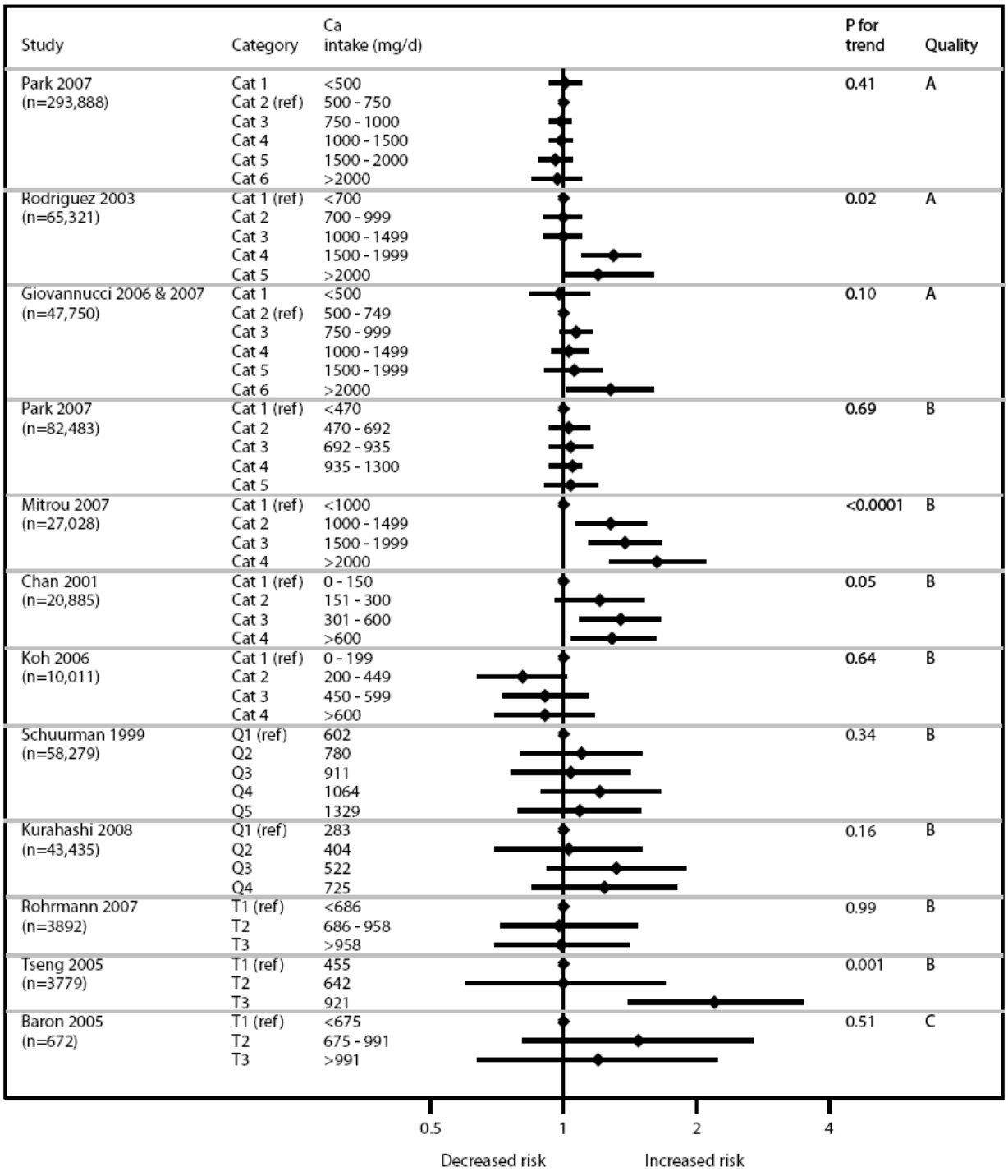
Author Year Study Name [PMID]	Life Stage (male), y	Outcome (n/N; Incidence)	Followup Duration	Total Ca intake in mg/d	No. of Cases	Total no. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Mitrou 2007[132] ATBC [17106437]	51-70	Prostate cancer (1267/27,028; 0.047)	≤17 y	<1000[A]	151	nd	**1**	**Reference**		
				1000-1499	611	nd	1.28	1.07, 1.54*	<0.0001	A
				1500-1999	402	nd	1.38	1.14, 1.67*		
				≥2000	103	nd	1.63	1.27, 2.10*		
Park 2007[133] MCS [17925283]	19-50 51-70	Prostate cancer (4404/82,483; 0.053)	8 y	<470	706	nd	**1**	**Reference**		
				470-692	925	nd	1.03	0.93, 1.15	0.69	B
				692-935	949	nd	1.04	0.93, 1.17		
				935-1300	936	nd	1.05	0.93, 1.18		
				≥1301	888	nd	1.04	0.91, 1.20		
Chan 2001[127] PHS [11566656]	51-70	Prostate cancer (1012/20,885; 0.048)	≤11 y	0-150[A]	155	nd	**1**	**Reference**		
				151-300	206	nd	1.21	0.96, 1.53	0.05	B
				301-600	377	nd	1.35	1.09, 1.66*		
				>600	274	nd	1.29	1.04, 1.62*		
Koh 2006[130] HAH [17106437]	51-70	Prostate cancer (815/10,011; 0.081)	≤10 y	0-199[A]	209	nd	**1**	**Reference**		
				200-449	167	nd	0.81	0.64, 1.02	0.64	
				450-599	238	nd	0.91	0.73, 1.14		
				≥600	201	nd	0.91	0.70, 1.18		B
		Mortality Prostate cancer		0-199	30	nd	**1.00**	**Reference**		
				200-449	21	nd	0.57	0.27, 1.19	0.52	
				450-599	23	nd	0.60	0.29, 1.22		
				≥600	25	nd	0.81	0.38, 1.71		
Schuurman 1999[137] Netherlands Cohort [10362125]	51-70	Prostate cancer (704/58,279; 0.012)	≤6.3 y	602[A,B]	120	nd	**1**	**Reference**		
				780	126	nd	1.10	0.80, 1.51	0.34	B
				911	127	nd	1.04	0.76, 1.42		
				1064	140	nd	1.21	0.89, 1.66		
				1329	129	nd	1.09	0.79, 1.50		
Kurahashi 2008[131] Japan PHC [18398033]	19-50 51-70	Prostate cancer (329/43,435; 0.008)	≤7.5 y	283[A,B]	56	nd	**1**	**Reference**		
				404	68	nd	1.03	0.70, 1.51	0.16	B
				522	98	nd	1.32	0.92, 1.90		
				725	107	nd	1.24	0.85, 1.81		
Rohrmann 2007[136] WCC [17315319]	51-70	Prostate cancer (199/3892; 0.051)	≤15 y	<686	58	nd	**1**	**Reference**		
				686-958	65	nd	0.98	0.72, 1.47	0.99	B
				>958	76	nd	0.99[C]	0.70, 1.41		

Continued

Author Year Study Name [PMID]	Life Stage (male), y	Outcome (n/N; Incidence)	Followup Duration	Total Ca intake in mg/d	No. of Cases	Total no. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Tseng 2005[138] NHEFS [15883441]	51-70	Prostate cancer (131/3779; 0.035)	7.7 y	455[B]	28	nd	**1**	**Reference**	0.001	B
				642	37	nd	1.0	0.6, 1.7		
				921	66	nd	2.2	1.4, 3.5*		
Baron 2005[56] CPP [15767334]	51-70	Prostate cancer (70/672; 0.10)	≤12 y	<675[A,B]	nd	nd	**1**	**Reference**	0.51	C
				675-991	nd	nd	1.48	0.81, 2.70		
				>991	nd	nd	1.20	0.64, 2.23		

* Statistically significant (P<0.05)
[A] Dietary calcium
[B] median of tertile, quartile or quintile
[C] Adjusted hazard ratio

Figure 13. Prostate cancer risk stratified by calcium intake



Colorectal cancer.

Synopsis.

This synopsis is based on one systematic review, 19 cohort studies in 20 publications, and one nested case-control study. The systematic review of two RCTs that evaluated high risk population found no difference in colorectal cancer incidence between those participants who received supplemental calcium and those who did not. Among five cohort studies and one nested case-control study with methodological quality B, two cohort studies showed a significant inverse association between total calcium intake and colorectal cancer. Among 14 cohort studies with methodological quality C, five studies showed a significant inverse association between total calcium intake and colorectal cancer, one found an inverse association between total calcium intake and colon cancer, and two showed an inverse association between calcium and rectal cancer. All the studies that found a significant association recruited men or women who were followed for a period that ranged between 1.4 and 11.3 years. None of these studies included participants younger than 45 years.

Detailed presentation (Tables 60, 61, 62 & 63; Figures 14, 15, 16, 17 & 18)

One systematic review of two RCTs of supplemental calcium on prevention of recurrent colorectal adenoma comprising 1346 adults (mean age 59 to 61 years) examined colorectal cancer incidence.[139] A fixed-effects model meta-analysis found no significant difference in colorectal cancer incidence between supplemental calcium and no supplements. This meta-analysis is considered inconclusive because only 5 colorectal cancer cases were diagnosed during the study period.

Nineteen cohort studies in 20 publications[125,140-158] and one nested case-control study[159] evaluated the association between calcium intake and colorectal, colon, or rectal cancer. Sample sizes ranged from 1954 to 492,810. Half of the studies were conducted in the US (latitude ranged from 21° N to 54° N),[125,140,142,144,145,147,150-152,154,155,158] one study was conducted in China (latitude 31° N),[149] and the rest were conducted in Europe including France (latitude 46° N),[141] the Netherlands (latitude 52° N),[159] the United Kingdom (latitude ranged between 54° N and 55° N),[156] and Scandinavia (latitude ranged between 59° N and 69° N).[143,146,148,153,157] For colorectal cancer, the incidence ranged from 0.003 to 0.025 for cohorts, while in the nested case-control study, the colorectal cancer incidence was 0.142; for colon cancer, the incidence ranged from 0.003 to 0.024; and for rectal cancer, the incidence ranged from 0.003 to 0.004. The participants' mean age ranged from 7.6 to 61.9 years. Average followup ranged from 1.4 to 19.6 years. Only one study reported that exposure assessors were blinded to outcome.[154] No studies mentioned that outcome assessors were blinded to exposure. None of the studies reported power calculations. The majority of the studies evaluated the potential effect of various factors besides calcium on colorectal cancer. All performed analyses adjusted at least for age. Except for four studies[151,156-158] that used dietary history, all other studies used a food frequency questionnaire to assess dietary intake. More than half of the studies did not confirm all or part of cancer cases with pathology reports. Six studies[125,140-143,159] were rated B, and 15 publications[144-158] were rated C for methodological quality.

Findings by age, sex and/or ethnicity.

One cohort study analyzed a total of 4374 children (IQR 4-11 years old) living in the United Kingdom. It found no significant association between total calcium intake and colorectal cancer in these children after 65 years of followup.[156]

One cohort study analyzed a total of 127,749 adults aged between 50 and 74 years old living in US. It found an inverse association between total calcium intake and colorectal cancer.[145] However, another cohort study and one nested case-control study did not find such an association.[157,159] The only cohort study that analyzed subjects older than 15 years did not find a significant association between total calcium intake and colon cancer as well as rectal cancer in subgroup analyses.[157] Out of seven cohort studies[125,140,143-145,148,154] that analyzed male adults older than 40 years living in US, or Scandinavia, five[125,143-145,148] found an inverse association between total calcium intake and colorectal cancer. Out of eleven cohort studies[125,140-142,144-147,149,154,155] that analyzed women, four[125,144,146,147] found an inverse association between total calcium intake and colorectal cancer.

Out of four cohort studies[145,148,151,153] that analyzed men, one[145] found an inverse association between total calcium intake and colon cancer in a subgroup analysis. Out of four cohort studies[146,147,150,153] that analyzed women, none found an association between total calcium intake and colon cancer. For rectal cancer, one[148] of two[145,148] studies that analyzed men and one[152] of three[146,147,152] studies that analyzed women found an inverse association between total calcium intake and rectal cancer.[148,152]

One cohort study in the US found an inverse association between total calcium intake and colorectal cancer in a subgroup analysis of Japanese Americans aged 45 to 75 years, and a borderline inverse association in Caucasians of the same age range; however, the same cohort study did not find any significant association in subgroup analyses of African Americans, Native Hawaiians, and Latinos.[144] Another cohort study in the US that recruited only Japanese American men living in Hawaii did not find an association between total calcium intake and colon cancer.[151] One cohort study did not find any association in Chinese women (aged 40 to 70 years) living in Shanghai,[149]

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** One study that followed up children with an interquartile range of age of 4 to 11 years for 65 years found no significant association between total calcium intake at baseline and the risk of colorectal cancer.
- **9 – 18 y** Three studies included some children and/or adolescents in this life stage, but no studies adequately evaluated this life stage.
- **19 – 50 y** Four studies included people with a mean or median age ranging from 39 to 50 years. No significant association was found between total calcium intake and colorectal cancer risk. Ten additional studies may have included participants in this life stage; however in these studies, no conclusions are possible for the subgroup in this life stage.
- **51 – 70 y** One inconclusive meta-analysis of 2 RCTs in adults with previous adenomatous polyps (mean age 59-61 years) found no significant difference in colorectal cancer incidence between those who were and those who were not supplemented at followup. Ten studies included people with a mean or median age ranged from 53 to 69

years. An association between higher total calcium intake and lower colorectal cancer risk was found in three studies in men and two studies in women. Another study of women found an association between higher total calcium intake and lower rectal cancer risk. Ten additional studies may also have included participants in this life stage An association between higher total calcium intake and lower colorectal cancer risk was found in two studies in men and two studies in women. However in these studies, the results are inconclusive for the subgroup in this life stage.

- **71+** One study that specifically included people in the retirement community found no association between total calcium intake and colorectal cancer risk. Nine additional studies may have also recruited participants in this life stage; however in these studies, no conclusions are possible for the subgroup in this life stage.
- **Postmenopause** One study focused on postmenopausal women. This study found an association between higher calcium intake and lower rectal cancer risk. However, it did not find any association for colon cancer risk.
- **Pregnant & lactating women** No data

Table 60. Systematic review of calcium supplementation and colorectal cancer incidence or adenoma recurrence

Author Year [PMID]	Weingarten, 2008[139] [18254022]
Design	Randomized controlled trials: Cochrane Library Issue 2, 2007, the Cochrane Colorectal Cancer Group (CCCG) specialized register, MEDLINE (1966 to July 2007), Cancerlit (1963 to April 2002), Embase (1980 to July 2007)
Population	Healthy adults and studies of adults at higher risk of colon cancer due to family history, previous adenomatous polyps, or inflammatory bowel disease
Intervention (Exposure) and Comparator	Calcium (>1200 mg/d) vs. placebo
Results	Calcium vs. placebo Colorectal cancer incidence: OR 0.34, CI 0.05-2.15, P=0.20 (I^2=0%) Colorectal adenoma recurrence: OR 0.74; 95%CI 0.58, 0.95, P=0.02 (I^2=0%) At least one adverse event requiring discontinuation: OR 0.93; 95% CI 0.42, 2.05, P=0.80
Comments	Based only on two RCTs (1346 participants). Heterogeneity due to different dose of supplementation (one RCT supplemented with 1200 mg/d and the other RCT with 2000 mg/d). Analysis based on fixed effects model; however, considering there are only two studies, random effects model might have been more appropriate. The result of no significant difference in colorectal cancer incidence is inconclusive since there were only 5 colorectal cancer cases during the study period. Analysis on adverse events is based only on reported data of one out of the two RCTs (Barron 1999).[160] Only participants with high risk due to previous adenomas were recruited in these two RCTs; therefore, applicability of the results can only be considered for high risk population. Insufficient evidence to recommend the general use of calcium supplements to prevent colorectal adenoma or colorectal cancer

AMSTAR			
A priori design?	X	**Study quality assessment performed?**	X
Two independent reviewers?	X	**Study quality appropriately used in analysis?**	X
Comprehensive literature search?	X	**Appropriate statistical synthesis?**	X
All publication types and languages included?		**Publication bias assessed?**	
Included and excluded studies listed?	X	**Conflicts of interest stated?**	X
Study characteristics provided?	X		

Table 61. Calcium and colorectal cancer: Characteristics of observational studies

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
Cohort												
Park, 2009[125] NIH-AARP Diet & Health (various) US [19237724]	• Health status • Mean age range, yr • Male (%)	Generally healthy men and women 50-71 60	• Dietary assessment method • Internal validation? (y/n)	Semi-quantitative FFQ (NCI-DHQ) y	CRC across 5 categories of total calcium intake	X	X	X	X		X	White Male ~92%; Female ~89%; Total Ca (both)
Wu, 2002[140] HPFS NHS (various) US [11904316]	• Health status • Mean age (range/SD), yr • Male (%)	HPFS: generally healthy male health professionals NHS: generally healthy female nurses HPFS: 54.4 NHS: 46.6 HPFS: 100 NHS: 0	• Dietary assessment method • Internal validation? (y/n)	HPFS: 131-item semi-quantitative FFQ (by Willet) NHS: 61-item semi-quantitative FFQ (by Willet) y	For HPFS, NHS separately: CRC across 7 categories of cumulative average calcium intake	X	X	X	X		X	Total Ca (both)
Kesse, 2005[141] Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy women 52.7 0	• Dietary assessment method • Internal validation? (y/n)	FFQ y	CRC across total calcium intake quartiles	X	X	X			X	Total Ca (food)
Lin, 2005[142] WHS US (various) [15800268]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy women nd 0	• Dietary assessment method • Internal validation? (y/n)	131-item FFQ y	CRC across total calcium intake quintiles	X	X	X	X		X	Total Ca (both)

continued

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
Pietinen, 1999[143] ATBC Finland (~64°N) [10530608]	• Health status	Generally healthy men; smokers	• Dietary assessment method	276-item FFQ	CRC across total calcium intake quartiles	X	X	X			X	Total Ca (food)
	• Mean age (range/SD), yr	Median, cases: 60.1; non cases: 57.1										
	• Male (%)	100	• Internal validation? (y/n)	y								
Park, 2007[144] The Multiethnic Cohort Study US (various) [17215380]	• Health status	Generally healthy men and women	• Dietary assessment method	FFQ	CRC per gender across total calcium intake quintiles	X	X	X	X		X	Total Ca (both)
	• Mean age (range/SD), yr	nd										
	• Male (%)	45	• Internal validation? (y/n)	y								
McCullough, 2003[145] CPS II US (various) [12708719]	• Health status	Generally healthy men and women	• Dietary assessment method	68-item semi-quantitative FFQ (modification of the brief Health Habits and History Questionnaire (HHHQ) by Block)	CRC across total calcium intake quintiles Subgroup analyses per gender For men, subgroup analyses per site (colon, rectal)	X	X	X	X		X	Total Ca (both)
	• Mean age (range/SD), yr	nd										
	• Male (%)	48	• Internal validation? (y/n)	y								
Shin, 2006[149] Shanghai Women's Health Study China (31°N) [17019716]	• Health status	Generally healthy women	• Dietary assessment method	77-item FFQ used in Shanghai Women's Health Study	CRC across total calcium intake quintiles Subgroup analyses per site (colon, rectal)	X	X		X		X	Chinese; Total Ca (food)
	• Mean age (range/SD), yr	Cases: 59 (8.5); non-cases: 52 (9.1)										
	• Male (%)	0	• Internal validation? (y/n)	y								

continued

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
Terry, 2002[146] Swedish Mammography Screening Cohort Sweden (59°N) [12467133]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy women nd 0	• Dietary assessment method • Internal validation? (y/n)	Self-administered 67-item FFQ y	CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal) Subgroup analyses per age (< 55 vs. ≥ 55 years old) and site (colon, rectal)	X	X	X			X	Total Ca (food)
Gaard,1996[153] nd Norway (60°-69°N) [9061275]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men and women 43 49	• Dietary assessment method • Internal validation? (y/n)	semi-quantitative FFQ (Oslo University) y	Colon cancer per gender across total calcium intake quartiles		X	X			X	Total Ca (food)
Flood, 2005[147] The Breast Cancer Detection Demonstration Project (BCDDP) US (various) [15668485]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy women 61.9 0	• Dietary assessment method • Internal validation? (y/n)	62-item semi-quantitative FFQ (by Block) y	CRC cancer across total calcium intake quintiles Subgroup analyses per site (colon, rectal)	X	X	X	X		X	Total Ca (both)
Larsson, 2006[148] The Cohort of Swedish Men Sweden (59°N) [16522915]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men 60.3 100	• Dietary assessment method • Internal validation? (y/n)	96-item semi-quantitative FFQ y	CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal)	X	X	X	X		X	Total Ca (both)
Bostick, 1993[150] Iowa Women's Health Study US (40°N) [8333412]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy post-menopausal women 61.5 0	• Dietary assessment method • Internal validation? (y/n)	127-item semi-quantitative FFQ (by Willet) y	Colon cancer across total calcium intake quintiles	X	X	X				Same cohort as Zheng 1998; Total Ca (both)

continued

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
Zheng, 1998[152] Iowa Women's Health Study US (40°N) [9521437]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy post-menopausal women 61.5 0	• Dietary assessment method • Internal validation? (y/n)	127-item semi-quantitative FFQ (by Willet) y	Rectal cancer across total calcium intake tertiles	X	X	X	X		X	Same cohort as Bostick 1993; Total Ca (both)
Kato, 1997[155] New York University Women's Health Study US (various) [9343837]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy women nd 0	• Dietary assessment method • Internal validation? (y/n)	70-item semi-quantitative FFQ (slightly modified from Block's) y	CRC across total calcium intake quartiles	X	X					Total Ca (food)
Wu, 1987[154] US (21°N) [3620314]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men and women nd 33	• Dietary assessment method • Internal validation? (y/n)	56-item FFQ n	CRC per gender across total calcium intake tertiles		X					Total Ca (dairy)
Jarvinen, 2001[157] nd Finland (64°N) [11641750]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men and women 39.1 nd	• Dietary assessment method • Internal validation? (y/n)	Diet history y	CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal)	X	X	X			X	Total Ca (food)
Stemmerman n, 1990[151] Japan Hawaii Cancer Study US (21°N) [2311461]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men nd 100	• Dietary assessment method • Internal validation? (y/n)	24-hour diet recall interview y	Colon cancer across total calcium intake tertiles		X					Japanese; Total Ca (food)

continued

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
van der Pols, 2007[156] The Boyd Orr Cohort UK (54°-55°N) [8333412]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy children 7.6 49.5	• Dietary assessment method • Internal validation? (y/n)	7-day household inventory method n	CRC between lowest and highest total calcium intake groups	X	X	X			X	Total Ca (food)
Garland, 1985[158] Western Electric Health Study US (41°N) [2857364]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men 48.7 (4.4) 100	• Dietary assessment method • Internal validation? (y/n)	28-day diet histories n	CRC across total calcium intake quartiles	X	X	X			X	Total Ca (food)
Nested case-control												
Kampman, 1994[159] The Netherlands Cohort Study Netherlands (52°N) [8205538]	• Health status • Mean age (range/SD), yr • Male (%)	Generally healthy men and women nd nd	• Dietary assessment method • Internal validation? (y/n)	150-item semi-quantitative FFQ y	CRC across total calcium intake quintiles	X	X		X		X	Total Ca (food)

Table 62. Calcium and colorectal cancer: Results of cohort studies

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Park, 2009[125] NIH-AARP Diet & Health US (various) [19237724]	Male adult (50-71 y)	CRC (nd)	**526**	nd	nd	84 mo	**1.0**	**Reference**	0.001	B
		CRC (nd)	498	nd	nd	84 mo	0.89	0.80, 0.98*		
		CRC (nd)	857	nd	nd	84 mo	0.83	0.75, 0.93*		
		CRC (nd)	1073	nd	nd	84 mo	0.87	0.78, 0.97*		
		CRC (nd)	1530	nd	nd	84 mo	0.79	0.70, 0.89*		
	Female adult (50-71 y)	CRC (nd)	**494**	nd	nd	84 mo	**1.0**	**Reference**	0.001	
		CRC (nd)	717	nd	nd	84 mo	0.87	0.75, 1.01		
		CRC (nd)	969	nd	nd	84 mo	0.83	0.71, 0.97*		
		CRC (nd)	1296	nd	nd	84 mo	0.71	0.60, 0.84*		
		CRC (nd)	1881	nd	nd	84 mo	0.72	0.61, 0.86*		
Wu 2002[140] HPFS: Health Professionals Follow-up Study NHS: Nurses' Health Study US (various) [11904316]	Male adult (40-75 y)	CRC (nd)	**≤ 500**	47	nd	nd	**1.0**	**Reference**	0.17	B
		CRC (nd)	501-600	48	nd	nd	0.69	0.46, 1.04		
		CRC (nd)	601-700	58	nd	nd	0.69	0.47, 1.01		
		CRC (nd)	701-800	51	nd	nd	0.60	0.40, 0.90*		
		CRC (nd)	801-1000	81	nd	nd	0.67	0.47, 0.97*		
		CRC (nd)	1001-1250	84	nd	nd	0.62	0.42, 0.92*		
		CRC (nd)	>1250	60	nd	nd	0.64	0.43, 0.95*		
	Female adult (30-55 y)	CRC (nd)	**≤ 500**	70	nd	nd	**1.0**	**Reference**	0.35	
		CRC (nd)	501-600	79	nd	nd	1.19	0.86, 1.64		
		CRC (nd)	601-700	83	nd	nd	1.07	0.77, 1.47		
		CRC (nd)	701-800	90	nd	nd	1.18	0.86, 1.63		
		CRC (nd)	801-1000	130	nd	nd	1.04	0.77, 1.40		
		CRC (nd)	1001-1250	106	nd	nd	1.05	0.77, 1.44		
		CRC (nd)	>1250	68	nd	nd	0.94	0.66, 1.33		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Kesse 2005[141] Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532]	Female adult (40-65 y)	CRC (nd)	**<766.22**	163	nd	82.8 mo	**1.0**	**Reference**	0.08	B
		CRC (nd)	766.22-962.63	154	nd	82.8 mo	0.94	0.63, 1.41		
		CRC (nd)	962.63-1201.81	150	nd	82.8 mo	0.78	0.51, 1.19		
		CRC (nd)	> 1201.81	131	nd	82.8 mo	0.72	0.47, 1.10		
Lin 2005[142] The Women's Health Study US (various) [15800268]	Female adult (≥ 45 y)	CRC (41/7691; 0.01)	**<614**	41	7691	120 mo	**1.0**	**Reference**	0.21	B
		CRC (nd)	614-785	31	nd	120 mo	0.74	0.46, 1.18		
		CRC (0.01)	785-1016	52	7690	120 mo	1.19	0.78, 1.81		
		CRC (nd)	1016-1357	41	nd	120 mo	0.92	0.58, 1.44		
		CRC (58/7690; 0.01)	> 1357	58	7690	120 mo	1.20	0.79, 1.85		
Pietinen 1999[143] ATBC Finland (~64°N) [10530608]	Male adult (50-69 y)	CRC (nd)	**Median Q1, 856**	60	nd	96 mo	**1.0**	**Reference**	0.04	B
		CRC (nd)	Median Q2, 1241	41	nd	96 mo	0.7	0.5, 1.0		
		CRC (nd)	Median Q3, 1484	45	nd	96 mo	0.7	0.5, 1.1		
		CRC (nd)	Median Q4, 1789	39	nd	96 mo	0.6	0.6, 0.9*		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Park 2007[144] The Multiethnic Cohort Study US (various) [17215380]	Male adult (45-75 y)	CRC (nd)	**< 288 /1000 kcal**	342	nd	87.6 mo	**1.0**	**Reference**	0.006	C
		CRC (nd)	288-369 /1000 kcal	271	nd	87.6 mo	1.02	0.86, 1.22		
		CRC (nd)	369-457 /1000 kcal	258	nd	87.6 mo	1.08	0.89, 1.31		
		CRC (nd)	457-611 /1000 kcal	177	nd	87.6 mo	0.85	0.68, 1.07		
		CRC (nd)	≥ 611 /1000 kcal	90	nd	87.6 mo	0.70	0.52, 0.93*		
	Female adult (45-75 y)	CRC (nd)	**< 288 /1000 kcal**	172	nd	87.6 mo	**1.0**	**Reference**	0.003	
		CRC (nd)	288-369 /1000 kcal	175	nd	87.6 mo	0.77	0.60, 0.97*		
		CRC (nd)	369-457 /1000 kcal	194	nd	87.6 mo	0.76	0.60, 0.97*		
		CRC (nd)	457-611 /1000 kcal	197	nd	87.6 mo	0.74	0.57, 0.94*		
		CRC (nd)	≥ 611 /1000 kcal	234	nd	87.6 mo	0.64	0.50, 0.83*		
McCullough 2003[145] CPS II US (various) [12708719]	Adult (50-74 y)	CRC (nd)	**<561**	156	nd	nd	**1.0**	**Reference**	0.02	C
		CRC (nd)	561-731	165	nd	nd	1.05	0.84, 1.31		
		CRC (nd)	732-925	137	nd	nd	0.88	0.70, 1.12		
		CRC (nd)	926-1255	108	nd	nd	0.72	0.56, 0.93*		
		CRC (nd)	>1255	117	nd	nd	0.87	0.67, 1.12		
	Male adult (50-74 y)	CRC (nd)	**<561**	89	nd	nd	**1.0**	**Reference**	0.04	
		CRC (nd)	561-731	106	nd	nd	1.01	0.76, 1.34		
		CRC (nd)	732-925	98	nd	nd	0.93	0.70, 1.25		
		CRC (nd)	926-1255	70	nd	nd	0.71	0.52, 0.98*		
		CRC (nd)	>1255	58	nd	nd	0.82	0.58, 1.16		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
		Colon cancer (nd)	**<561**	64	nd	nd	**1.0**	**Reference**	0.02	
		Colon cancer (nd)	561-731	82	nd	nd	1.08	0.77, 1.50*		
		Colon cancer (nd)	732-925	67	nd	nd	0.89	0.63, 1.27*		
		Colon cancer (nd)	926-1255	51	nd	nd	0.72	0.49, 1.05*		
		Colon cancer (nd)	>1255	38	nd	nd	0.74	0.49, 1.12*		
		Rectal cancer (nd)	**<561**	23	nd	nd	**1.0**	**Reference**	0.71	
		Rectal cancer (nd)	561-731	22	nd	nd	0.78	0.43, 1.41		
		Rectal cancer (nd)	732-925	29	nd	nd	1.02	0.58, 1.79		
		Rectal cancer (nd)	926-1255	16	nd	nd	0.60	0.31, 1.16		
		Rectal cancer (nd)	>1255	19	nd	nd	1.01	0.53, 1.93		
	Female adult (50-74 y)	CRC (nd)	**<561**	67	nd	nd	**1.0**	**Reference**	0.31	
		CRC (nd)	561-731	59	nd	nd	1.16	0.82, 1.66		
		CRC (nd)	732-925	39	nd	nd	0.80	0.54, 1.21		
		CRC (nd)	926-1255	38	nd	nd	0.78	0.51, 1.18		
		CRC (nd)	>1255	59	nd	nd	0.94	0.63, 1.39		
Shin 2006[149] Shanghai Women's Health Study China (31°N) [17019716]	Female adult (40-70)	CRC (nd)	**≤ 291.9**	nd	nd	Median, 68.9 mo	**1.0**	**Reference**	0.48	C
		CRC (nd)	≤ 389.9	nd	nd	Median, 68.9 mo	1.0	0.7, 1.4		
		CRC (nd)	≤ 488.2	nd	nd	Median, 68.9 mo	1.0	0.7, 1.4		
		CRC (nd)	≤ 610.8	nd	nd	Median, 68.9 mo	0.9	0.6, 1.3		
		CRC (nd)	> 610.8	nd	nd	Median, 68.9 mo	0.9	0.6, 1.3		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Terry 2002[146] Swedish Mammography Screening Cohort Sweden (59°N) [12467133]	Female adult (≤ 76 y)	CRC (nd)	**Mean (SD) Q1, 486 (79)**	156	nd	135.6 mo	**1.0**	**Reference**	0.02	C
		CRC (nd)	Mean (SD) Q2, 631 (34)	149	nd	135.6 mo	0.97	0.77, 1.21		
		CRC (nd)	Mean (SD) Q3, 747 (37)	145	nd	135.6 mo	0.95	0.75, 1.20		
		CRC (nd)	Mean (SD) Q4, 914 (136)	122	nd	135.6 mo	0.72	0.56, 0.93*		
		Colon cancer (nd)	**Mean (SD) Q1, 486 (79)**	100	nd	135.6 mo	**1.0**	**Reference**	0.06	
		Colon cancer (nd)	Mean (SD) Q2, 631 (34)	97	nd	135.6 mo	0.97	0.74, 1.30		
		Colon cancer (nd)	Mean (SD) Q3, 747 (37)	92	nd	135.6 mo	0.93	0.70, 1.24		
		Colon cancer (nd)	Mean (SD) Q4, 914 (136)	82	nd	135.6 mo	0.74	0.54, 1.01		
		Rectal cancer (nd)	**Mean (SD) Q1, 486 (79)**	55	nd	135.6 mo	**1.0**	**Reference**	0.12	
		Rectal cancer (nd)	Mean (SD) Q2, 631 (34)	48	nd	135.6 mo	0.89	0.60, 1.32		
		Rectal cancer (nd)	Mean (SD) Q3, 747 (37)	49	nd	135.6 mo	0.94	0.63, 1.39		
		Rectal cancer (nd)	Mean (SD) Q4, 914 (136)	39	nd	135.6 mo	0.70	0.45, 1.09		
	Female adult (< 55 y)	CRC (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.77	
		CRC (nd)	568-688	nd	nd	135.6 mo	1.06	0.68, 1.66		
		CRC (nd)	688-816	nd	nd	135.6 mo	1.11	0.71, 1.73		
		CRC (nd)	816-1300	nd	nd	135.6 mo	0.91	0.56, 1.48		
	Female adult (≥ 55 y)	CRC (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.008	
		CRC (nd)	568-688	nd	nd	135.6 mo	0.93	0.71, 1.21		
		CRC (nd)	688-816	nd	nd	135.6 mo	0.89	0.68, 1.17		
		CRC (nd)	816-1300	nd	nd	135.6 mo	0.66	0.49, 0.89*		
	Female adult (< 55 y)	Colon cancer (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.92	
		Colon cancer (nd)	568-688	nd	nd	135.6 mo	1.32	0.75 2.30		
		Colon cancer (nd)	688-816	nd	nd	135.6 mo	1.02	0.55, 1.85		
		Colon cancer (nd)	816-1300	nd	nd	135.6 mo	1.11	0.60, 2.05		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
	Female adult (≥ 55 y)	Colon cancer (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.02	
		Colon cancer (nd)	568-688	nd	nd	135.6 mo	0.89	0.64, 1.23		
		Colon cancer (nd)	688-816	nd	nd	135.6 mo	0.91	0.65, 1.26		
		Colon cancer (nd)	816-1300	nd	nd	135.6 mo	0.64	0.44, 0.92*		
	Female adult (< 55 y)	Rectal cancer (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.75	
		Rectal cancer (nd)	568-688	nd	nd	135.6 mo	0.33	0.34, 1.59		
		Rectal cancer (nd)	688-816	nd	nd	135.6 mo	1.30	0.66, 2.56		
		Rectal cancer (nd)	816-1300	nd	nd	135.6 mo	0.70	0.31, 1.62		
	Female adult (≥ 55 y)	Rectal cancer (nd)	**176-568**	nd	nd	135.6 mo	**1.0**	**Reference**	0.15	
		Rectal cancer (nd)	568-688	nd	nd	135.6 mo	0.96	0.61, 1.52		
		Rectal cancer (nd)	688-816	nd	nd	135.6 mo	0.79	0.48, 1.29		
		Rectal cancer (nd)	816-1300	nd	nd	135.6 mo	0.70	0.42, 1.19		
Gaard 1996[153] Norway (60°-69°N) [9061275]	Male adult (20-53 y)	Colon cancer (nd)	**<758**	22	nd	134.4 mo	**1.0**	**Reference**	0.15	C
		Colon cancer (nd)	759-912	24	nd	134.4 mo	1.02	0.57, 1.83		
		Colon cancer (nd)	913-1066	24	nd	134.4 mo	1.04	0.58, 1.86		
		Colon cancer (nd)	>1067	13	nd	134.4 mo	0.57	0.29, 1.13		
	Female adult (20-53 y)	Colon cancer (nd)	**<527**	15	nd	134.4 mo	**1.0**	**Reference**	0.94	
		Colon cancer (nd)	528-628	20	nd	134.4 mo	1.25	0.63, 2.46		
		Colon cancer (nd)	629-743	7	nd	134.4 mo	0.46	0.19, 1.12		
		Colon cancer (nd)	>744	18	nd	134.4 mo	1.20	0.60, 2.39		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Flood 2005[147] The Breast Cancer Detection Demonstration Project (BCDDP) US (various) [15668485]	Female adult (nd)	CRC (nd)	**<472**	102	nd	17 mo	**1.0**	**Reference**	0.02	C
		CRC (nd)	472-635	110	nd	17 mo	1.03	0.79, 1.35		
		CRC (nd)	636-844	86	nd	17 mo	0.80	0.60, 1.06		
		CRC (nd)	845-1270	106	nd	17 mo	0.96	0.73, 1.26		
		CRC (nd)	>1270	80	nd	17 mo	0.74	0.55, 0.99*		
		Colon cancer (nd)	**<472**	nd	nd	17 mo	**1.0**	**Reference**	0.10	
		Colon cancer (nd)	472-635	nd	nd	17 mo	0.84	0.59, 1.18		
		Colon cancer (nd)	636-844	nd	nd	17 mo	0.66	0.46, 0.96*		
		Colon cancer (nd)	845-1270	nd	nd	17 mo	0.78	0.55, 1.11		
		Colon cancer (nd)	>1270	nd	nd	17 mo	0.69	0.48, 0.99*		
		Rectal cancer (nd)	**<472**	nd	nd	17 mo	**1.0**	**Reference**	0.30	
		Rectal cancer (nd)	472-635	nd	nd	17 mo	1.19	0.57, 2.48		
		Rectal cancer (nd)	636-844	nd	nd	17 mo	1.10	0.52, 2.32		
		Rectal cancer (nd)	845-1270	nd	nd	17 mo	1.23	0.60, 2.53		
		Rectal cancer (nd)	>1270	nd	nd	17 mo	0.93	0.43, 2.01		
Larsson 2006[148] The Cohort of Swedish Men Sweden (59°N) [16522915]	Male adult (45-79 y)	CRC (111/11,341; 0.011)	**<956**	127	11,348	80.4 mo	**1.0**	**Reference**	0.01	C
		CRC (107/11295; 0.010)	956-1179	111	11,341	80.4 mo	0.80	0.61, 1.04		
		CRC (104/11,322; 0.009)	1180-1444	107	11,295	80.4 mo	0.73	0.56, 0.96*		
		CRC (67/11,322; 0.009)	>1445	104	11,322	80.4 mo	0.68	0.51, 0.91*		
		Colon cancer (77/11,348; 0.006)	**<956**	67	11,322	80.4 mo	0.72	0.50, 1.04	0.15	
		Colon cancer (70/11,295; 0.007)	956-1179	77	11,348	80.4 mo	**1.0**	**Reference**		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
		Colon cancer (67/11,322; 0.006)	1180-1444	70	11,295	80.4 mo	0.80	0.57, 1.12		
		Colon cancer (50/11,348; 0.006)	>1445	67	11,322	80.4 mo	0.72	0.50, 1.04		
		Rectal cancer (49/11,341; 0.004)	**<956**	50	11,348	80.4 mo	**1.0**	**Reference**	0.02	
		Rectal cancer (37/11,295; 0.004)	956-1179	49	11,341	80.4 mo	0.91	0.61, 1.37		
		Rectal cancer (37/11,322; 0.003)	1180-1444	37	11,295	80.4 mo	0.63	0.40, 0.98*		
		Rectal cancer (37/11,322; 0.003)	>1445	37	11,322	80.4 mo	0.61	0.38, 0.98*		
Bostick 1993[150] Iowa Women's Health Study US (40°N) [8333412]	Female adult (55-69 y)	Colon cancer (nd)	**<629**	54	nd	nd	**1.0**	**Reference**	0.22	
		Colon cancer (nd)	629-896	44	nd	nd	0.89	0.59, 1.33		
		Colon cancer (nd)	897-1188	42	nd	nd	0.88	0.58, 1.33		
		Colon cancer (nd)	1189-1547	44	nd	nd	0.97	0.63, 1.50		
		Colon cancer (nd)	>1548	28	nd	nd	0.68	0.41, 1.11		
Zheng 1998[152] Iowa Women's Health Study US (40°N) [9521437]	Female adult, (55-69 y)	Rectal cancer (nd)	**<800.8**	56	nd	108 mo	**1.0**	**Reference**	0.02	C
		Rectal cancer (nd)	800.8-1278.7	52	nd	108 mo	0.90	0.61, 1.33		
		Rectal cancer (nd)	≥1278.7	36	nd	108 mo	0.59	0.37, 0.94*		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Kato 1997[155] New York University Women's Health Study US (various) [9343837]	Female adult (34-65 y)	CRC (nd)	**Lowest, Q1 (nd)**	nd	nd	85.2 mo	**1.0**	**Reference**	0.18	C
		CRC (nd)	Q2 (nd)	nd	nd	85.2 mo	1.15	0.67, 1.95		
		CRC (nd)	Q3 (nd)	nd	nd	85.2 mo	0.90	0.52, 1.57		
		CRC (nd)	Highest Q4 (nd)	nd	nd	85.2 mo	0.71	0.39, 1.28		
Wu 1987[154] US (21°N) [3620314]	Male adult (nd)	CRC (nd)	**Low tertile (nd)**	nd	nd	nd	**1.0**	**Reference**	ns	C
		CRC (nd)	Medium tertile (nd)	nd	nd	nd	1.19	0.6, 2.2		
		CRC (nd)	High tertile (nd)	nd	nd	nd	0.86	0.4, 1.7		
	Female adult (nd)	CRC (nd)	**Low tertile (nd)**	nd	nd	nd	**1.0**	**Reference**	ns	
		CRC (nd)	Medium tertile (nd)	nd	nd	nd	0.9	0.5, 1.6		
		CRC (nd)	High tertile (nd)	nd	nd	nd	0.89	0.5, 1.6		
Jarvinen 2001[157] Finland (64°N) [11641750]	Adolescent and adult (> 15 y)	CRC (nd)	**Male: <1178.2 Female: <862.5**	20	nd	235.2 mo	**1.0**	**Reference**	0.97	C
		CRC (nd)	Male: 1178.2-1557.1 Female: 862.5-1110.7	19	nd	235.2 mo	1.17	0.60, 2.27		
		CRC (nd)	Male: 1557.2-1953.2 Female: 1110.8-1416.6	18	nd	235.2 mo	1.37	0.67, 2.81		
		CRC (nd)	Male: > 1953.3 Female: > 1416.7	15	nd	235.2 mo	1.43	0.61, 3.39		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
		Colon cancer (nd)	**Male: <1178.2 Female: <862.5**	10	nd	235.2 mo	**1.0**	**Reference**	0.17	
		Colon cancer (nd)	Male: 1178.2-1557.1 Female: 862.5-1110.7	14	nd	235.2 mo	1.44	0.61, 3.39		
		Colon cancer (nd)	Male: 1557.2-1953.2 Female: 1110.8-1416.6	9	nd	235.2 mo	1.04	0.38, 2.83		
		Colon cancer (nd)	Male: > 1953.3 Female: > 1416.7	5	nd	235.2 mo	0.63	0.17, 2.35		
		Rectal cancer (nd)	**Male: <1178.2 Female: <862.5**	10	nd	235.2 mo	**1.0**	**Reference**	0.19	
		Rectal cancer (nd)	Male: 1178.2-1557.1 Female: 862.5-1110.7	5	nd	235.2 mo	0.77	0.25, 2.37		
		Rectal cancer (nd)	Male: 1557.2-1953.2 Female: 1110.8-1416.6	9	nd	235.2 mo	1.88	0.67, 5.30		
		Rectal cancer (nd)	Male: > 1953.3 Female: > 1416.7	10	nd	235.2 mo	3.01	0.93, 9.73		

continued

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Stemmermann 1990[151] Japan Hawaii Cancer Study US (21°N) [2311461]	Male adult (nd)	Colon cancer (74/2466; 0.02)	Low (nd)	74	2466	nd	1.3	0.9, 1.8	0.16	C
		Colon cancer (57/2456; 0.02)	Medium (nd)	57	2456	nd	1.0	0.7, 1.4		
		Colon cancer (58/2461; 0.03)	High (nd)	58	2461	nd	**1.0**	**Reference**		
van der Pols 2007[156] The Boyd Orr Cohort UK (54°-55°N) [8333412]	Children (IQR 4-11 y)	CRC (nd)	Lowest Q1, (nd)	nd	nd	nd	**1.0**	**Reference**	0.18	C
		CRC (nd)	Highest Q4, (nd)	nd	nd	nd	1.91	0.84, 4.32		
Garland 1985[158] Western Electric Health Study US (41°N) [2857364]	Male adult (40-55 y)	CRC (19/488; 0.04)	102-241 /1000 kcal	19	488	nd	nd	nd	nd	C
		CRC (12/489; 0.02)	242-306 /1000kcal	12	489	nd	nd	nd		
		CRC (12/489; 0.02)	307-383 /1000 kcal	12	489	nd	nd	nd		
		CRC (6/458; 0.01)	384-906 /1000 kcal	6	458	nd	nd	nd		

Table 63. Calcium and colorectal cancer: Results of nested case-control studies

Author Year Study Name Location (Latitude) PMID	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Kampman 1994[159] The Netherlands Cohort Study Netherlands (52°N) [8205538]	Adult (55-69 y)	CRC (443/3111, 0.14)	Median Q1, 596	98	623	39.6 mo	**1.0**	**Reference**	0.89	B
			Median Q2, 768	89	619	39.6 mo	0.83	0.58, 1.22		
			Median Q3, 893	87	622	39.6 mo	0.96	0.67, 1.39		
			Median Q4, 1032	81	627	39.6 mo	0.93	0.64, 1.36		
			Median Q5, 1288	88	620	39.6 mo	0.92	0.64, 1.34		

Figure 14 Colorectal cancer risk in both sexes stratified by calcium intake

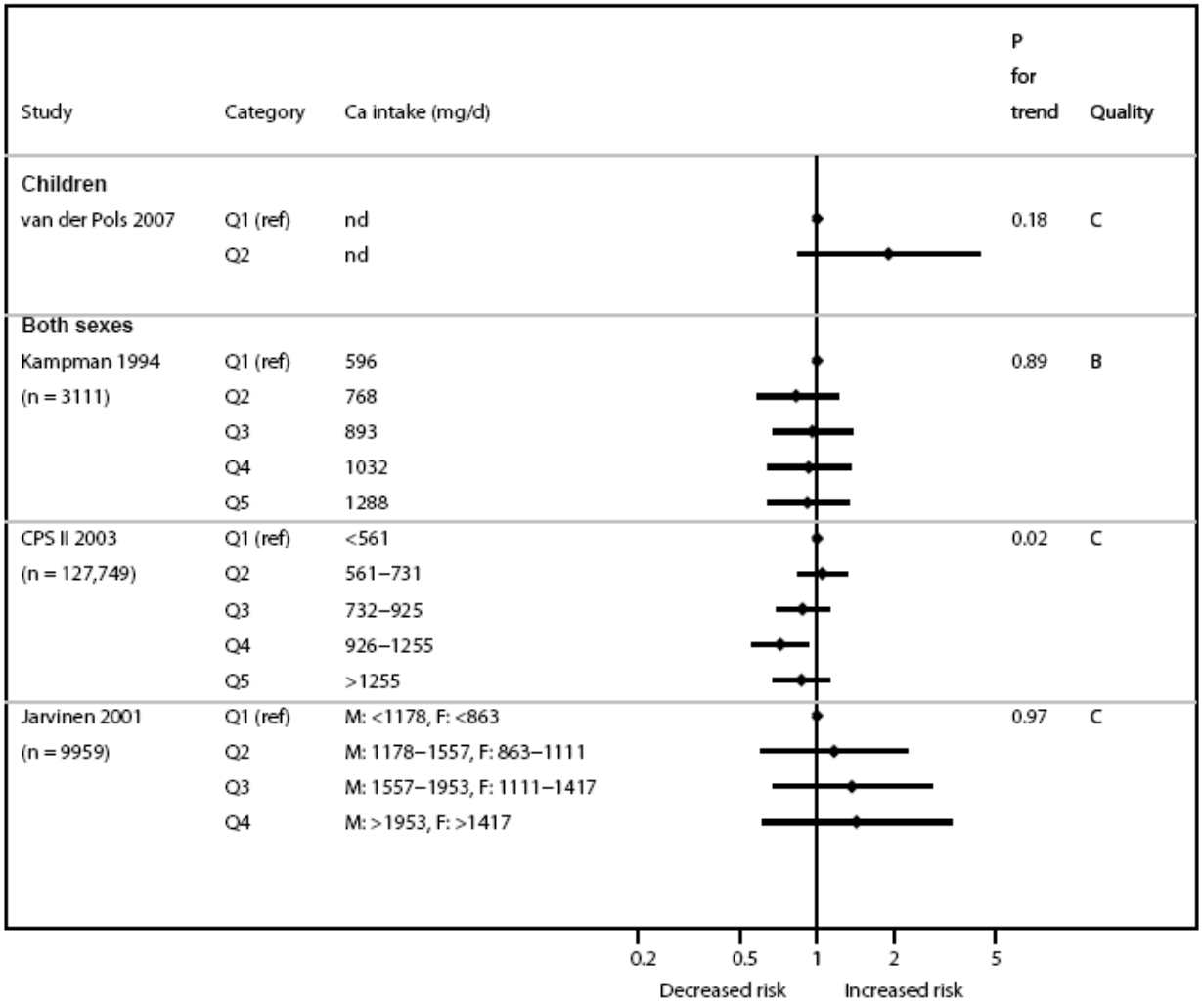


Figure 15 Colorectal cancer risk in men stratified by calcium intake

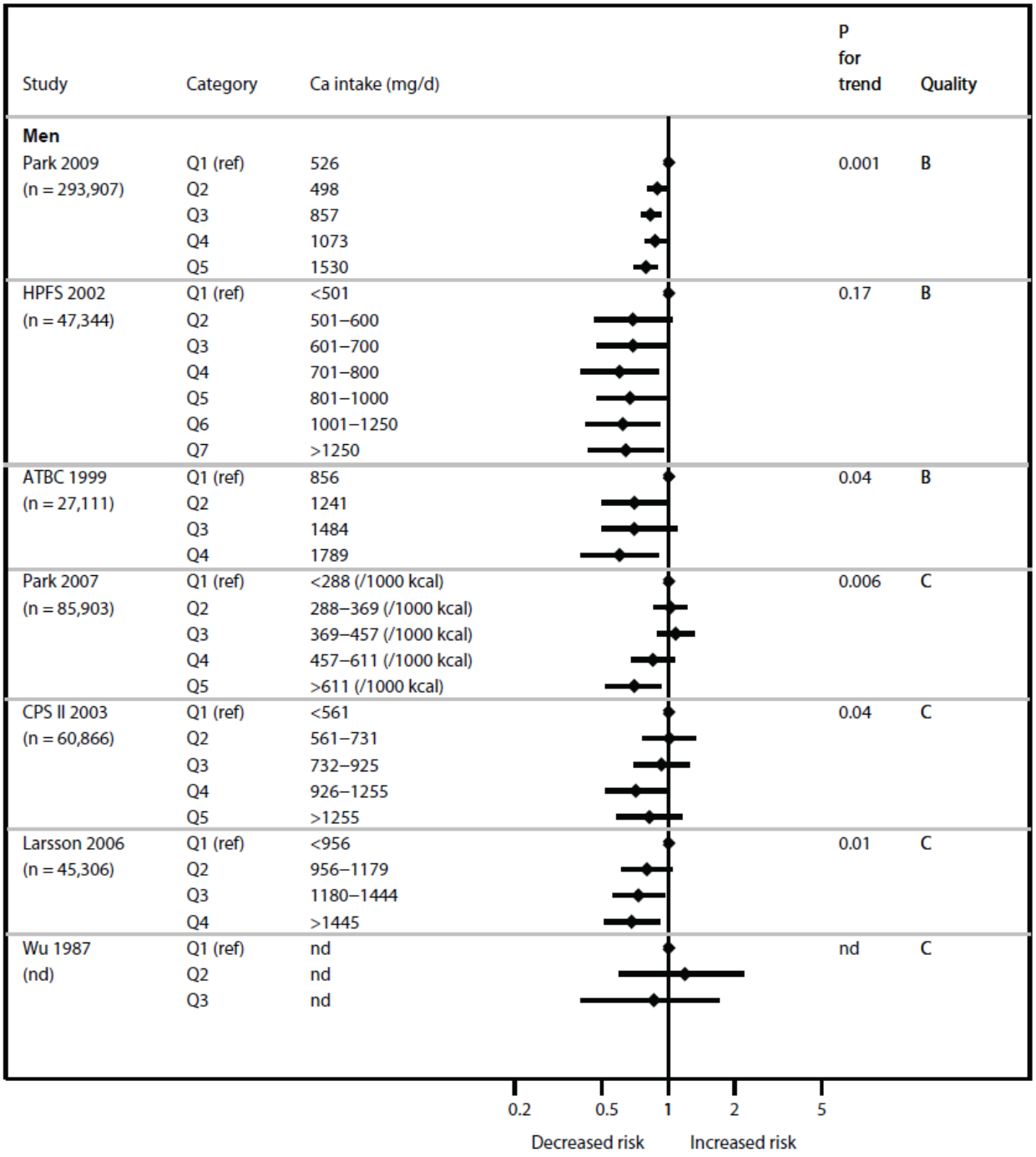


Figure 16 Colorectal cancer risk in women stratified by calcium intake

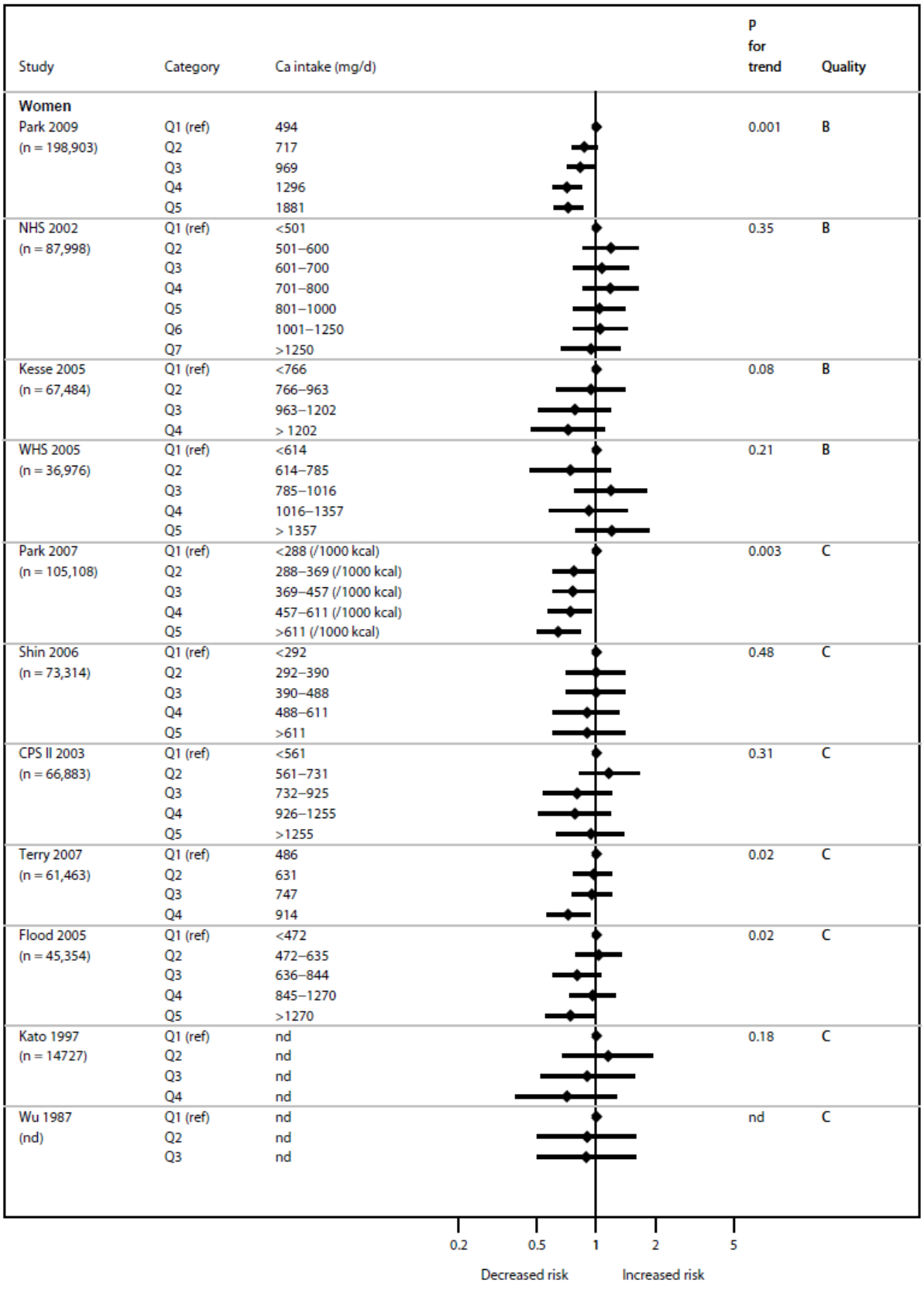


Figure 17 Colon cancer risk stratified by calcium intake

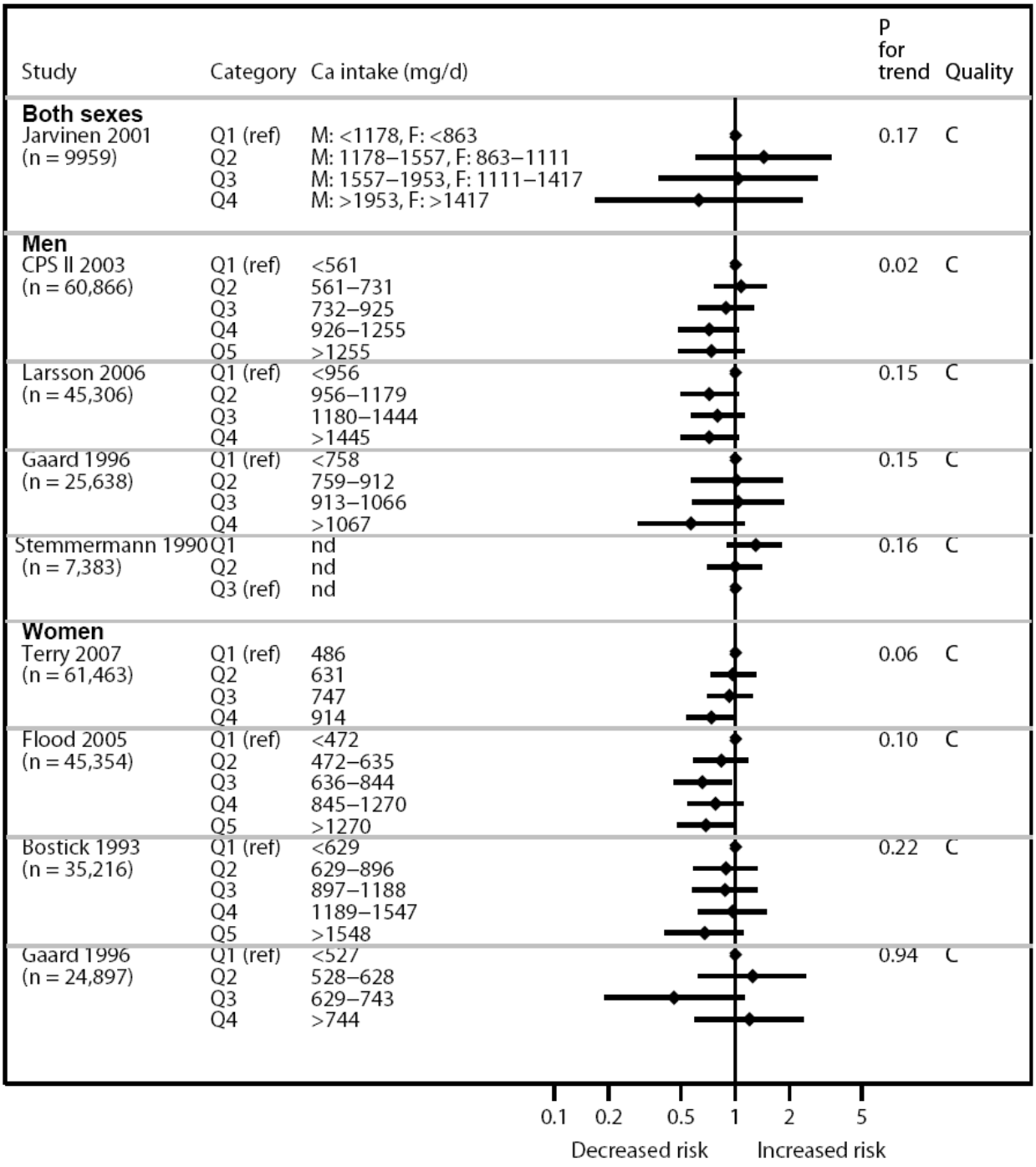
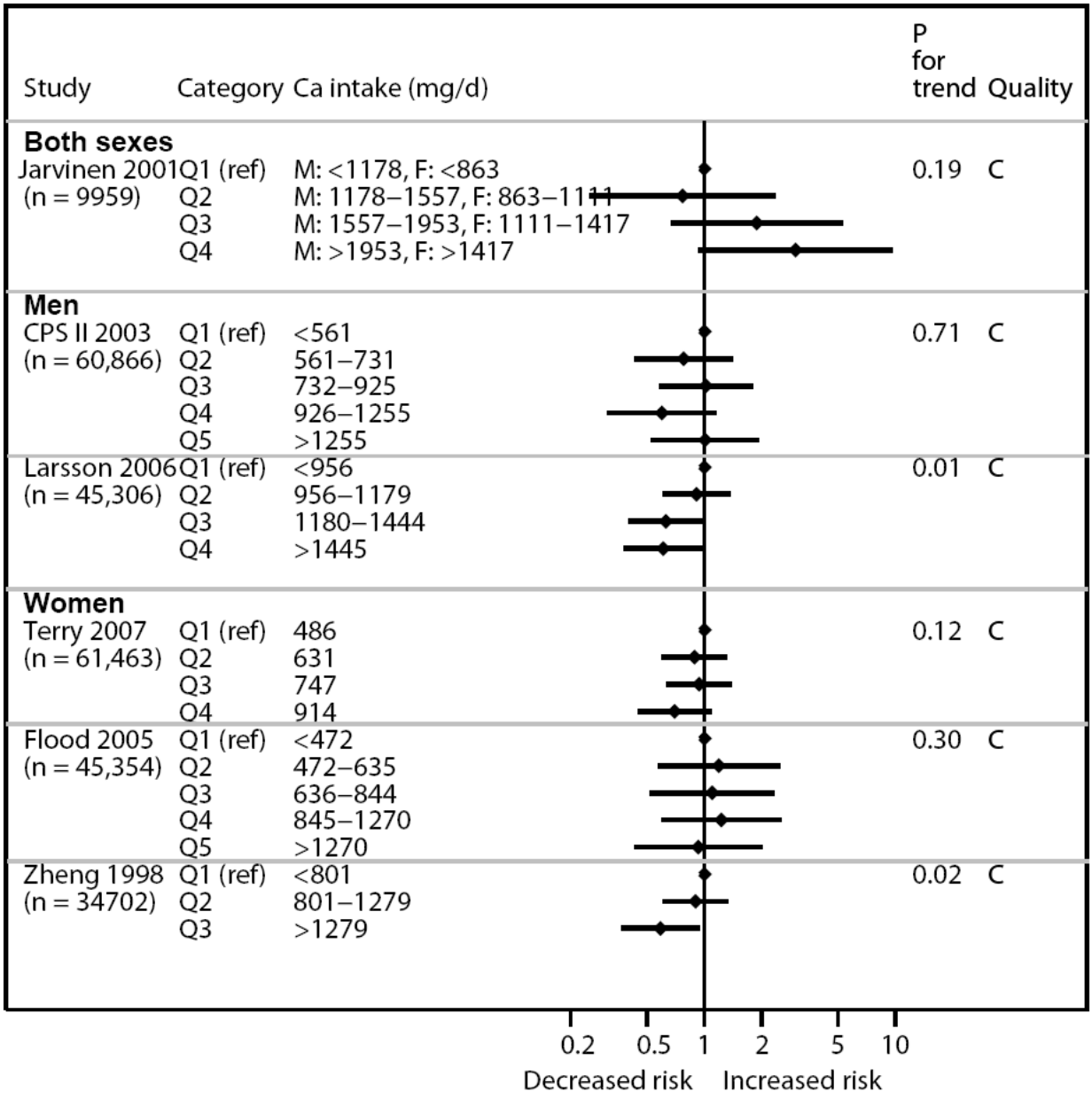


Figure 18. Rectal cancer risk stratified by calcium intake



Colorectal adenoma.

Synopsis.

This synopsis is based on one systematic review, two comparative trials (one post hoc followup study of an RCT and one nonrandomized trial), and four cohort studies. The systematic review that included two RCTs which evaluated high risk population for the prevention of colorectal adenoma recurrence showed a reduction in the risk of colorectal adenoma with calcium supplementation (OR 0.74, 95 percent CI 0.58, 0.95; P=0.02). The B quality long-term followup study of an RCT of calcium supplementation (1200 mg/d) versus placebo in healthy adults showed no significant difference in the risk of recurrence of colorectal adenoma. The nonrandomized comparative trial (methodological quality C) also found a significant reduction in adenoma recurrence risk among healthy adults who received calcium supplementation. Among four cohort studies (methodological quality B), two found an inverse association between total calcium intake and the risk of colorectal adenoma, while the others found no significant association.

Detailed presentation (Tables 64, 65, 66, 67 & 68; Figure 19).

One systematic review included two RCTs that recruited high risk population for colorectal adenoma due to previous adenomatous polyps.[139] A total of 1346 participants were analyzed for the effect of calcium supplementation (1200 to 2000 mg elemental calcium daily). The odds ratio of colorectal adenoma recurrence was 0.74 (95 percent CI 0.58, 0.95; P=0.02), comparing calcium supplementation to the placebo. A B quality post hoc followup analysis[161] of one of the two RCTs that were included in the meta-analysis examined the long-term effect of calcium supplementation to prevent colorectal adenoma recurrence. The trial recruited participants with previous colorectal adenoma, and compared the preventative efficacy of calcium supplementation (1200 mg/d) to placebo. Adenoma recurrence at 4 years was the original primary outcome. During the followup period after the trial treatment, about 50 percent of participants in both groups took some calcium supplements. In 347 participants who underwent colonoscopy during the first 5 years after the intervention period, the relative risk of adenoma recurrence was 0.63 (95 percent CI 0.46, 0.87; P=0.005) comparing calcium supplementation to placebo, whereas no difference was found in 424 participants who underwent colonoscopy in the subsequent 5 to 10 years after the trial treatment.

A nonrandomized comparative study[162] presented the percentage of adenoma recurrence in a group of men and women who underwent polypectomy, and received calcium supplementation (2000 mg/d) as chemoprevention. The same study also presented the percentage of adenoma recurrence in a group of men and women who underwent polypectomy but were not supplemented with calcium. The intervention group included 175 participants while the nonsupplemented group included nine patients. The two groups were followed for an average of 3.1 years. The trial was rated C for methodological quality. In this study,[162] the percentage of participants with adenoma recurrence was lower in the intervention group compared to the nonsupplemented participants (13 percent versus 55 percent); however, no further statistical analysis was provided.

Four cohort studies evaluated the association between calcium intake and colorectal adenoma.[141,163-165] Three studies were conducted in the US (latitude range between 33°N and 38°N), and one in France (latitude 46°N). Sample sizes ranged from 1304 to 48,115. Two studies recruited participants with a history of colorectal adenoma, and the other two recruited

healthy subjects without a history of adenoma. The incidence rate of colorectal adenomas ranged between 0.003 and 0.025. The participants' mean age ranged from 52.7 to 61.1 years. Average followup ranged from 36.8 to 44.4 months. Three of the four studies did not report information on assessor blinding.[141,164,165] All studies assessed dietary intake with food frequency questionnaires and confirmed cases with pathology reports. The quality of all four studies was rated B.

Findings by age and sex.

One cohort study[165] that analyzed men and women (aged 40-80 y) with a history of colorectal adenoma found an inverse association between total calcium intake and colorectal adenoma recurrence after an average of 3.1 years of followup (RR 0.62, highest [>1279 mg/d] compared with lowest intake [<778 mg/d]; P for trend = 0.005). The study did not test statistically whether the strength of the association differed between men and women. Another study of both men and women with previous adenomatous polyps found no significant association between total calcium intake and colorectal adenoma recurrence.

One cohort study that analyzed exclusively women (aged 40-65 y) without a history of colorectal adenoma found an inverse association between total calcium intake and colorectal adenoma (RR 0.80, highest [>1226 mg/d] compared with lowest intake [<786 mg/d]; P for trend = 0.04).[141] Another study of women without previous adenomatous polyps found no significant association.[163]

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** One cohort study of women age 30 to 55 years found no association between total calcium intakes and colorectal adenoma. Three additional studies included some men or women in this life stage. Two of these studies reported a significant inverse association between total calcium intake and colorectal adenoma. However, their results are inconclusive for adults in this life stage.
- **51 – 70 y** One meta-analysis of 2 RCTs in adults with previous adenomatous polyps (mean age 59 to 61 years) found a significant decrease in colorectal adenoma recurrence in supplemental calcium (1200 to 2000 mg elemental calcium daily) compared to no supplements (odds ratio, 0.74 [95 percent CI 0.58, 0.95]; P=0.02). A long-term followup study of one of the two trials found no difference in recurrence after 5 to 10 years after the intervention. One nonrandomized comparative trial also found a significant reduction in adenoma recurrence risk among healthy adults with a mean age 55 years who received calcium supplementation compared to no supplements (13 percent vs. 55 percent; P value not reported). Two cohort studies evaluated participants with a mean age 53 and 61 years respectively. One additional study recruited adults in this life stage. Two of the three studies, one including adults with a history of adenoma and another including women without adenoma history, found an inverse association between total calcium intake and colorectal adenoma.
- **71+** No studies specifically focused on this life stage. Two studies also included some men and women with a history of adenoma corresponding to this life

stage. One found an inverse association between total calcium intake and colorectal adenoma, while the other did not find such an association.

- **Postmenopause** No data
- **Pregnant & lactating women** No data

Table 64. Calcium and colorectal adenoma: Characteristics of interventional studies

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Vit D & Ca Background Diets	Interventions	Compliance	Comments
RCTs						
Grau, 2007[161] Calcium Polyp Prevention Study[A] US (34°-44°N) [17227996]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy men and women with a recent colorectal adenoma 60.6 71.7	Calcium, mean: 876 mg/d[B]	Elemental calcium,1200 mg/d	nd	Duplicated with Wallace; results during the observational post-intervention phase (5-10 years)
Nonrandomized comparative study						
Duris, 1996[162] nd Slovakia (48°N) [8682453]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy men and women; history of adenomatous polyps after polypectomy 54.7 62	nd	Calcium carbonicum (2 g/d)		No statistical comparison between groups

[A] A post-hoc followup study (Calcium Follow-up Study) of a RCT (Calcium Polyp Prevention Study).

[B] Two percent of the participants in the both groups took calcium supplements during the intervention period. Forty-seven percent in the placebo group and 49 percent in the supplement arm took any calcium supplements during the followup period after the intervention. The dosage was not reported (based on the self-reported data in the earlier report).[160]

Table 65. Calcium and colorectal adenoma: Characteristics of cohort studies

Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	Seasons	Life styles	
Cohort												
Oh, 2007[163] The Nurses Health Study US (38°N) [17379616]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy women 30-55 0	• Dietary assessment method • Internal validation? (y/n)	61-item semi-quantitative FFQ (by Willet) y	Colorectal adenoma across total calcium intake quintiles	x	x	x	x		x	Total Ca (both)
Kesse, 2005[141] Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy women 52.7 0	• Dietary assessment method • Internal validation? (y/n)	FFQ y	Colorectal adenomas across total calcium intake quartiles	x	x	x			x	Total Ca (both)
Hartman, 2005[164] The Polyp Prevention Trial US (38° N) [15671222]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy men and women; history of at least one colorectal adenoma; 90% Caucasian 61.1 (9.9) 64	• Dietary assessment method • Internal validation? (y/n)	FFQ y	Adenoma recurrence across total calcium intake quintiles	x	x	x	x			Total Ca (both)
Martinez, 2002[165] Wheat Bran Fiber (WBF) trial US (33°N) [12020102]	• Health status • Mean age (range/SD), y • Male (%)	Generally healthy men and women; history of colorectal adenoma(s) nd 57.1	• Dietary assessment method • Internal validation? (y/n)	113-item Arizona Food Frequency Questionnaire (AFFQ) y	Adenoma recurrence across total calcium intake quartiles Subgroup analyses per gender	x	x		x			Total Ca (food)

Table 66. Calcium and colorectal adenoma recurrence: Results of RCTs

Author Year Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Grau 2007[161] Calcium Polyp Prevention Study US (various) [17227996]	Adult	All adenomas	1°	92.4	Calcium carbonate (1200 mg/d)	82	208	RR	1.09	0.85, 1.39	0.51	B
					Placebo	82	216					

Table 67. Calcium and colorectal adenoma recurrence: Results of nonrandomized comparative study

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Duris 1996[162] Slovakia (48°N) [8682453]	Adult (30-75 y)	Adenoma recurrence	nd	37.2	Calcium carbonicum, 2g/d	12	175	RR	nd	nd	nd	C
					No chemoprevention	5	9					

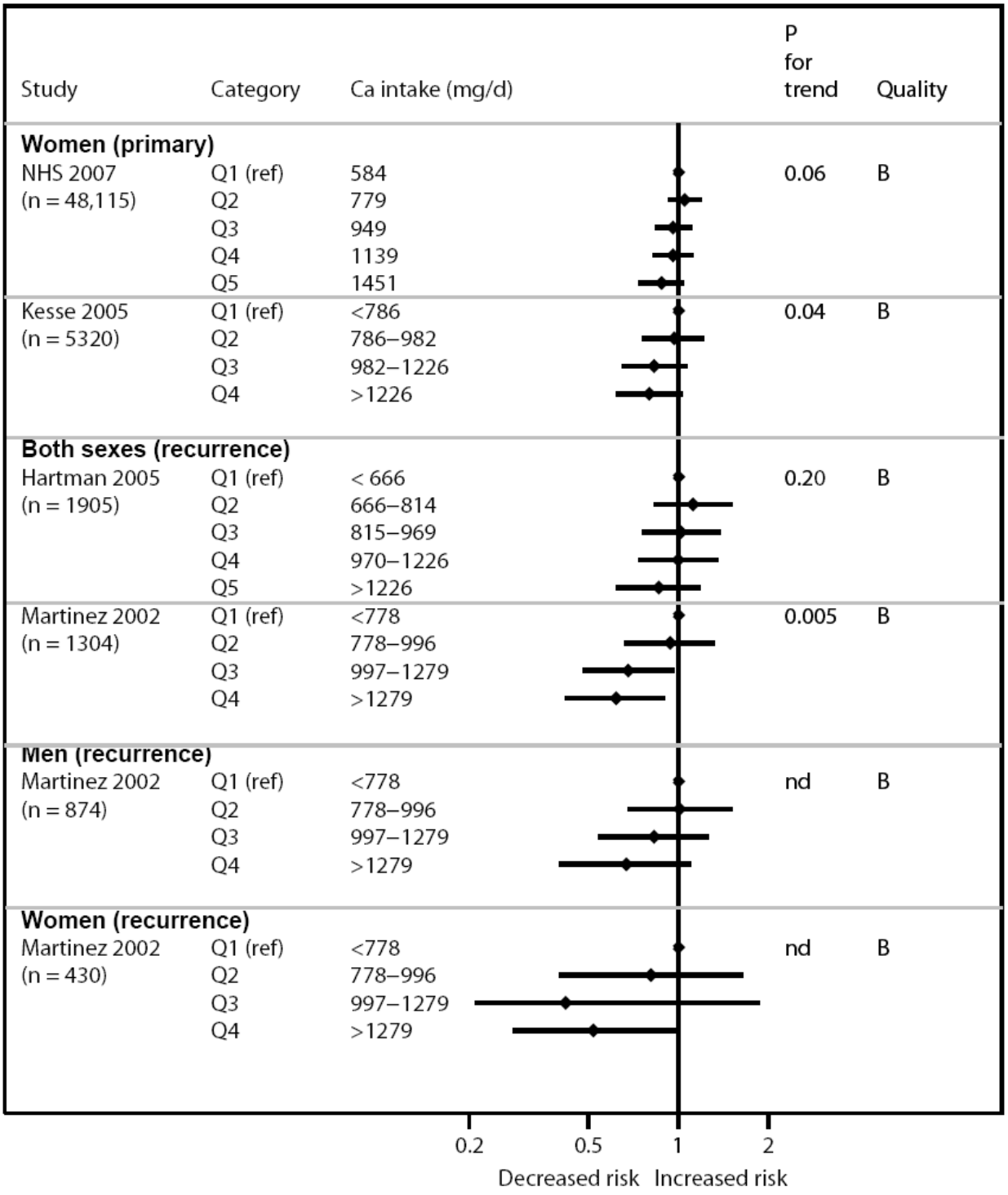
Table 68. Calcium and colorectal adenoma: Results of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Oh 2007[163] The Nurses Health Study US (38°N) [17379616]	Female adult (30-55 y)	Adenoma (nd)	**Median Q1, 584**	nd	nd	nd	**1.0**	**Reference**	0.06	B
		Adenoma (nd)	Median Q2, 779	nd	nd	nd	1.05	0.93, 1.20		
		Adenoma (nd)	Median Q3, 949	nd	nd	nd	0.96	0.84, 1.11		
		Adenoma (nd)	Median Q4, 1139	nd	nd	nd	0.96	0.82, 1.12		
		Adenoma (nd)	Median Q5, 1451	nd	nd	nd	0.88	0.74, 1.04		
Kesse 2005[141] Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532]	Female adult (40-65 y)	Adenoma (nd)	**<785.62**	154	nd	44.4 mo	**1.0**	**Reference**	0.04	B
		Adenoma (nd)	785.62-1226.16	150	nd	44.4 mo	0.97	0.76, 1.22		
		Adenoma (nd)	981.67-1226.16	131	nd	44.4 mo	0.83	0.65, 1.07		
		Adenoma (nd)	>1226.16	156	nd	44.4 mo	0.80	0.62, 1.03		
Hartman 2005[164] The Polyp Prevention Trial US (38° N) [15671222]	Adult (≥ 35 y)	Adenoma recurrence (nd)	**< 666**	156	nd	nd	**1.0**	**Reference**	0.20	B
		Adenoma recurrence (nd)	666-814	163	nd	nd	1.12	0.83, 1.51		
		Adenoma recurrence (nd)	815-969	154	nd	nd	1.02	0.76, 1.38		
		Adenoma recurrence (nd)	970-1226	150	nd	nd	1.00	0.74, 1.36		
		Adenoma recurrence (nd)	>1226	131	nd	nd	0.86	0.62, 1.18		

continued

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N, Incidence)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Follow up Duration (Time to Dx)	Adjusted RR	95% CI	P for Trend	Study Quality
Martinez 2002[165] Wheat Bran Fiber (WBF) trial US (38° N) [12020102]	Adult (40-80 y)	Adenoma recurrence (178/326; 0.55)	**< 778**	178	326	36.8 mo	**1.0**	**Reference**	0.005	B
		Adenoma recurrence (175/326; 0.54)	778-996	175	326	36.8 mo	0.94	0.66, 1.32		
		Adenoma recurrence (148/326; 0.45)	997-1279	148	326	36.8 mo	0.68	0.48, 0.97*		
		Adenoma recurrence (138/326; 0.42)	>1279	138	326	36.8 mo	0.62	0.42, 0.90*		
	Male adult (40-80 y)	Adenoma recurrence (nd)	**< 778**	nd	nd	36.8 mo	**1.0**	**Reference**	nd	
		Adenoma recurrence (nd)	778-996	nd	nd	36.8 mo	1.01	0.68, 1.51		
		Adenoma recurrence (nd)	997-1279	nd	nd	36.8 mo	0.83	0.54, 1.26		
		Adenoma recurrence (nd)	>1279	nd	nd	36.8 mo	0.67	0.40, 1.10		
	Female adult (40-80 y)	Adenoma recurrence (nd)	**< 778**	nd	nd	36.8 mo	**1.0**	**Reference**	nd	
		Adenoma recurrence (nd)	778-996	nd	nd	36.8 mo	0.81	0.40, 1.64		
		Adenoma recurrence (nd)	997-1279	nd	nd	36.8 mo	0.42	0.21, 1.87		
		Adenoma recurrence (nd)	>1279	nd	nd	36.8 mo	0.52	0.28, 0.98*		

Figure 19. Colorectal adenomatous polyp risk stratified by calcium intake



Breast cancer incidence.

Synopsis.

No qualified systematic reviews evaluated the association between dietary and supplemental calcium intake and the risk of breast cancer. No RCTs were identified. Six cohort studies compared calcium intake and the risk of breast cancer. In four studies, premenopausal women with calcium intakes in the range of 780-1750 mg/d had a decreased risk of incident breast cancer.[125,166-170] Only one study reported decreased risk of breast cancer in both premenopausal and postmenopausal women for calcium intake ranged from 1250 to 1750 mg/d compared with the lowest quintile of intake of less than 500 mg/d.[168] In two of six studies, there was no association between calcium intake and breast cancer (both overall and by menopausal status).[125,170] Five studies were rated B and one study rated C.

Detailed presentation (Tables 69 & 70; Figure 20).

Six studies recruited a total of 452,398 (ranged from 3600 to 198,903) pre-and postmenopausal women and followed them for a period of 7 to 16 years. The participants had an average age ranged from 47 to 63 years. Four studies conducted in the US and one study conducted in Sweden used validated food frequency questionnaire to quantify calcium intake levels. One study conducted in France used computerized questionnaire to quantify calcium intake levels. The incidence of breast cancer in these studies ranged from 2.5 to 4.8 percent. In four of the six cohort studies, premenopausal women with calcium intakes in the range of 780 to 1750 mg/d had a decreased risk of incident breast cancer compared to those with lowest quintile intake levels in each study. There was no association between calcium intake and breast cancer in the two of six studies.[125,170]

Findings by age and sex.

In subgroup analysis of four cohort studies, premenopausal women had a consistently decreased risk of breast cancer. No association was found for postmenopausal women.

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** A cohort study of Nurses' Health Study including women with an average age of 47 years had a decrease risk (RR 0.75, 95 percent CI 0.55, 0.99) in breast cancer among those with calcium intake levels of 1000-1250 mg/d compared to those with intake levels lesser than 500 mg/d.
- **51 – 70 y** Three of the five cohort studies of women with an average age between 51- 63 years, found a decreased risk of breast cancer among those with calcium intakes in the range of 780-1750 mg/d compared to those with lowest quintile intake levels in each study.
- **≥71 y** Not reviewed
- **Postmenopause** Cohort studies did not find an association between breast cancer risk and calcium intake levels among postmenopausal women.
- **Pregnant & lactating women** Not reviewed

Table 69. Calcium and breast cancer: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Park 2009 NIH-AARP US 38º N [19237724]	• Health status • Mean age (range/SD), y	No cancer 50-71	• Dietary assessment method • Internal validation? (y/n)	FFQ (NCI-DHQ) USDA Nutrient Database y	Quintile 1 vs. Quintile 2, 3, 4, 5	x	x	x	x		x	Total calcium intake from diet and supplement
Shin 2002[169] NHS US 38° N [12208895]	• Health status • Mean age (range/SD), y	No cancer 47 (ND)	• Dietary assessment method • Internal validation? (y/n)	61 item FFQ USDA Nutrient Database y	500 mg vs. 500-600, 600-700, 700-800, 800-1000, 1000-1250, >1250	x	x	x	x	x	x	Total calcium intake from diet and supplement
McCullough 2005[168] CPS II Nutrition Cohort US 38° N [16365007]	• Health status • Mean age (range/SD), y	No cancer 63 (ND)	• Dietary assessment method • Internal validation? (y/n)	Modified FFQ of Block et al. y	500 mg vs. 500-750, 750-1000, 1000-1250, 1250-1500, 1500-1750, >1750	x	x	x	x	x	x	Total calcium intake from diet and supplement
Larsson 2009[170] Swedish Mammography Cohort Sweden 62° N [19056569]	• Health status • Mean age (range/SD), y	No cancer 53.7 (9.7)	• Dietary assessment method • Internal validation? (y/n)	FFQ Swedish National Food Administration Database y	<727 vs. 727-862, 863-980, 980-1125, >1125	x	x	x		x	x	Total calcium intake from diet and supplement
Lin J 2007[167] WHS US 38º N [17533208]	• Health status • Mean age (range/SD), y	No cancer or CVD 55 (55-56)	• Dietary assessment method • Internal validation? (y/n)	Willet method USDA Nutrient Database y	Quintile 1 vs. Quintile 2, 3, 4, 5	x	x	x		x	x	Total calcium intake from diet and supplement

continued

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Kesse-Guyot 2007[166] SU.VI.MAX France 46° N [17536191]	• Health status • Mean age (range/SD), y	No cancer 51 (6.3)	• Dietary assessment method • Internal validation? (y/n)	Computerized questionnaires ND	Quintile 1 vs. Quintile 2, 3, 4	x	x	x		x	x	Dietary calcium intake

Table 70. Calcium and breast cancer: Results of cohort studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Park 2009[125] NIH-AARP [19237724]	Pre- and Post-menopausal women	Breast cancer (5856/198,903; 2.9%)	7 y	Q1	494	5856	**HR 1**	**Reference**	NS	B
				Q2	717	5856	0.96	0.88-1.04		
				Q3	969	5856	0.95	0.87-1.03		
				Q4	1296	5856	0.94	0.86-1.02		
				Q5	1881	5856	0.98	0.90-1.07		
Shin 2002[169] NHS [12208895]	Pre-menopausal women	Breast cancer (3172/88,381; 3.6%)	16 y	≤ 500	142	ND	**1**	**Reference**	0.05	B
				500-600	106	ND	0.88	0.68, 1.13		
				600-700	133	ND	0.97	0.76, 1.24		
				700-800	119	ND	0.95	0.74, 1.22		
				800-1000	161	ND	0.82	0.64, 1.05		
				1000-1250	104	ND	0.75	0.57, 0.99*		
				>1250	62	ND	0.80	0.58, 1.12		
	Post-menopausal women			≤ 500	240	ND	**1**	**Reference**	NS	
				500-600	216	ND	0.86	0.72, 1.04		
				600-700	293	ND	0.94	0.79, 1.12		
				700-800	292	ND	0.92	0.77, 1.10		
				800-1000	518	ND	0.93	0.79, 1.10		
				1000-1250	433	ND	0.90	0.76, 1.07		
				>1250	353	ND	0.93	0.77, 1.12		
McCullough 2005[168] CPS II Nutrition Cohort [16365007]	Pre- and Post-menopausal women	Breast cancer (2855/68,567; 4.1%)	8 y	≤500	457	10,620	**1**	**Reference**	0.07	B
				500-750	729	17,880	0.91	0.81, 1.02		
				750-1000	581	14,023	0.92	0.81, 1.04		
				1000-1250	407	9120	0.97	0.85, 1.11		
				1250-1500	248	6296	0.84	0.72, 0.98*		
				1500-1750	144	3983	0.76	0.63, 0.92*		
				1750	289	6645	0.91	0.79, 1.06		

continued

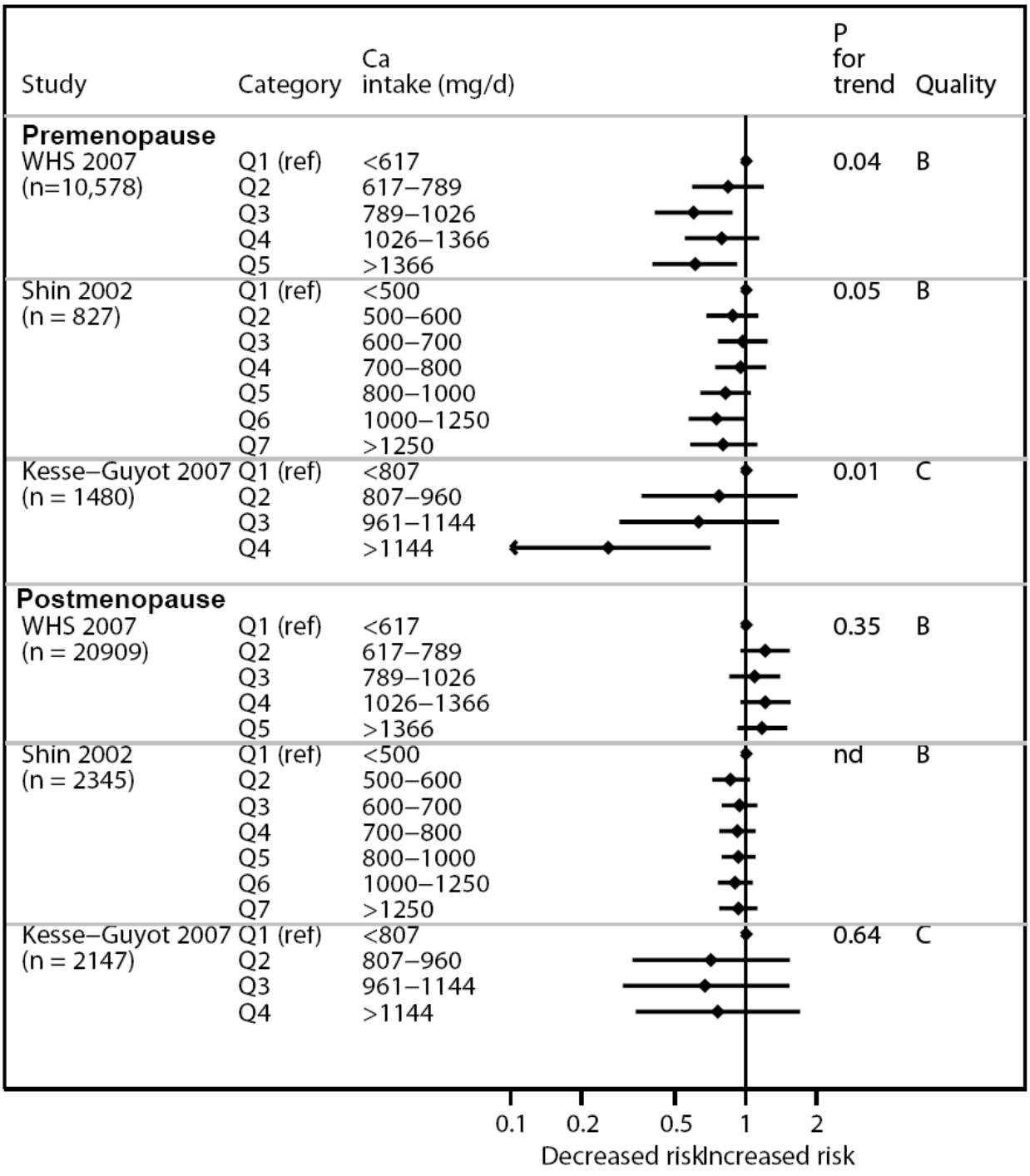
Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Larsson 2009[170] Swedish Mammography Cohort [19056569]	Pre- and Post-menopausal women	Invasive Breast cancer (2952/61,433; 4.8%)	9 y	<727	595	2952	**1**	**Reference**	NS	B
				727-862	595	2952	0.97	0.87-1.09		
				863-980	592	2952	0.95	0.84-1.06		
				980-1125	571	2952	0.93	0.83-1.04		
				>1125	599	2952	0.97	0.87-1.09		
Lin J 2007[167] WHS [17533208]	Pre-menopausal women	Invasive breast cancer (878/31,487; 2.8%)	10 y	<617	70	10,578	**HR 1**	**Reference**	.04	B
				617-789	65	10,578	0.84	0.59, 1.19		
				789-1026	44	10,578	0.60	0.41, 0.88*		
				1026-1366	59	10,578	0.79	0.55, 1.14		
				≥1366	38	10,578	0.61	0.40, 0.92*		
	Post-menopausal women			<617	104	20,909	**HR 1**	**Reference**	NS	
				617-789	116	20,909	1.21	0.95, 1.54		
				789-1026	112	20,909	1.09	0.85, 1.40		
				1026-1366	119	20,909	1.21	0.95, 1.55		
				≥1366	151	20,909	1.17	0.92, 1.50		
Kesse-Guyot 2007[166] SU.VI.MAX trial [17536191]	Pre- and Post-menopausal	Breast cancer (92/3627; 2.5%)	8 y	<807	32	3627	**1**	**Reference**	0.04	C
				807-960	24	3627	0.73	0.42, 1.25		
				961-1144	20	3627	0.65	0.37, 1.14		
				>1144	16	3627	0.50	0.27, 0.91*		
	Post-menopausal			<807	14	nd	**1**	**Reference**	0.64	
				807-960	13	nd	0.71	0.33, 1.54		
				961-1144	10	nd	0.67	0.30, 1.53		
				>1144	11	nd	0.76	0.34, 1.70		

continued

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
	Pre-menopausal			<807	18	nd	**1**	**Reference**	0.01	
				807-960	11	nd	0.77	0.36, 1.66		
				961-1144	10	nd	0.63	0.29, 1.38		
				>1144	5	nd	0.26	0.10, 0.71*		

HR: hazard ratio
*Statistically significant (P<0.05)

Figure 20. Breast cancer risk stratified by calcium intake



Breast Mammographic Density.

Synopsis.

No systematic reviews evaluated the association between dietary and supplemental calcium intake and breast mammographic density. No RCTs of calcium intake evaluated breast mammography density. One prospective cohort study evaluated the association of calcium intake and breast mammographic density.[171] Both premenopausal and postmenopausal women with calcium intakes in the range of 523 mg/d to greater than 1021 mg/d were followed for almost 40 years, and there was no association between calcium intake and breast mammographic density. The methodological quality of this study was rated B.

Detailed presentation (Tables 71 & 72).

One prospective cohort study followed from birth of a British national representative sample of 2547 women and followed them for a period of 53 years.[171] Women had an average age of 51.5 years. Dietary calcium intake was evaluated using 5-day food records. The breast density in women was assessed through mammography at the ages 36, 43, and 53 years. Since the measurement at the age of 53 years was cross-sectional, this has been excluded from our analyses. There was no linear association between dietary calcium intakes in the range of 523 mg/d to greater than 1021 mg/d and breast mammographic density.

Findings by age and sex.

In subgroup analysis by age categories, there was no linear association between calcium intake and breast mammography density.

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** There was no linear association between calcium intake in the range of 523 mg/d to greater than 1021 mg/d and breast mammographic density
- **51 – 70 y** No data
- **≥71 y** No data
- **Postmenopause** No data
- **Pregnant & lactating women** Not reviewed

Table 71. Calcium and breast mammography density: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Cohort												
Mishra 2008[171] Medical MRC NSHD UK 54º N [18827811]	• Health status • Mean age (range/SD), y	No breast cancer 52	• Dietary assessment method • Internal validation? (y/n)	5-day food diaries McCance and Widdowson's food table ND	At age 36 y: <523, 524-648, 652-784, 785-940, >941 At age 43 y: <611, 612-735, 736-859, 860-1020, >1021	x	x	x	x		x	Total calcium intake from diet and supplement

Table 72. Calcium and breast cancer: Results of cohort studies

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Mishra 2008[171] Medical MRC NSHD [18827811	Premenopausal women	Breast cancer density (nd; median 21.9%)	~32 y	≤523	133	766	β coefficient 1	Reference	NS	B
			~32 y	524 – 648	143	766	-0.11	-0.33, 0.10		
			~32 y	652 – 784	156	766	-0.05	-0.27, 0.17		
			~32 y	785 – 940	160	766	-0.04	-0.27, 0.19		
			~32 y	≥941	174	766	-0.08	-0.32, 0.17		
			~39 y	≤611	145	755	β coefficient 1	Reference	NS	
			~39 y	612-735	156	755	-0.13	-0.35, 0.09		
			~39 y	736-859	145	755	-0.06	-0.29, 0.17		
			~39 y	860-1020	156	755	-0.11	-0.34, 0.12		
			~39 y	≥1021	153	755	-0.16	-0.42, 0.09		

Pancreatic cancer.

We reviewed primary studies that evaluated associations between calcium intake and incidence of pancreatic cancer.

Synopsis.

Two studies analyzed three US cohorts and found that total daily calcium intake was not associated with the risk of pancreatic cancer in men and women. No RCTs of calcium intake or supplement have evaluated this outcome.

Detailed presentation (Tables 73 & 74).

One study analyzed data from Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS).[172] The study identified a total of 365 cases of pancreatic cancer (178/75,427 women aged 38 to 65 years from NHS; 178/46,771 men aged 40 to 75 years from HPFS). Comparing the group with at least 1000 mg/d of calcium intake to the group with less than 500 mg/d, there was no significant difference in the relative risk of pancreatic cancer (RR 0.94; 95 percent CI 0.62, 1.41 for overall; 0.75; 95 percent CI 0.43, 1.30 for NHS; 1.23; 95 percent CI 0.67, 2.25 for HPFS). The result was adjusted for age, categories of total vitamin D intake, smoking, diabetes, BMI, height, region of residence, use of multivitamin, and parity (for women). The pancreatic cancer was not stratified into endocrine versus exocrine tumors. Methodological quality of this study was rated A.

Another study analyzed data from AARP (the American Association of Retired Persons) members, aged 50 to 71 years old, living in six specific states in the US.[125] The study identified a total of 717 and 384 cases of pancreatic cancer in men and women over 7 years of followup period, respectively. Pancreatic cancer was one of many other cancer outcomes evaluated in this study. The results showed that that total calcium intake was not associated with the risk of pancreatic cancer after controlling for potential risk factors pertinent to individual cancers. The methodological quality of this study was rated B.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** One study analyzed two US cohorts (NHS [women 38 - 65 y] and HPFS [men 40 -75 y]) and found that total daily calcium intake was not associated with the risk of pancreatic cancer.
- **51 – 70 y** One study analyzed two US cohorts (NHS [women 38 - 65 y] and HPFS [men 40 -75 y]) and found that total daily calcium intake was not associated with the risk of pancreatic cancer. Another study analyzed US AARP cohort with men and women in this life stage found similar result.
- **≥71 y** One study that analyzed HPFS included males up to 75 years old and found that total daily calcium intake was not associated with the risk of pancreatic cancer.
- **Postmenopause** No data
- **Pregnant & lactating women** Not reviewed

Table 73. Calcium and pancreatic cancer: Characteristics of cohort studies

Author, Year Study Name Location (Latitude) [PMID]	Population		Dietary calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV exposure	Life styles	
Skinner 2006[172] NHS, HPFS US (multiple latitudes) [16985031]	Health status Mean age (range/SD), y Male (%)	DM: NHS 3%; HPFS 1% NHS 51; HPFS 55 NHS 0; HPFS 100	Dietary assessment method Internal validation? (y/n)	131-item FFQ (Willet, 1990) y	Pancreatic cancer risk stratified by different intakes of calcium (dietary and supplement combined)	X	X	X	X	X	X	current smoker ~23%
Park 2009[125] NIH-AARP US 38º N [19237724]	• Health status • Mean age (range/), y • Male (%)	No cancer 50-71 60	• Dietary assessment method • Internal validation? (y/n)	FFQ (NCI-DHQ) USDA Nutrient Database y	Pancreatic cancer risk stratified by quintile of total calcium intake	X	X	X	X		X	Total calcium intake from diet and supplement

Table 74. Calcium and pancreatic cancer: Results of cohort studies

Author Year Study Name [PMID]	Life Stage, y	Outcome (n/N; Incidence)	Followup Duration, y	Total Ca intake in mg/d	No. of Cases	Total no. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Skinner 2006[172] NHS, HPFS US (multiple latitudes) [16985031]	19-50 51-70 ≥71	Pancreatic cancer (365/122,198; 0.003) overall	14.5	<500	41	nd	**1**	**Reference**	0.29	A
				500-999	228	nd	1.17	0.83, 1.66		
				≥1000	96	nd	0.94	0.62, 1.41		
	19-50 51-70 women	Pancreatic cancer (178/75,427; 0.002) NHS	15.4	<500	24	nd	**1**	**Reference**	0.09	
				500-999	109	nd	1.09	0.69, 1.73		
				≥1000	45	nd	0.75	0.43, 1.30		
	19-50 51-70	Pancreatic cancer (187/46,771; 0.004)	13.1	<500	17	nd	**1**	**Reference**	0.86	
				500-999	119	nd	1.28	0.76, 2.18		

Author Year Study Name [PMID]	Life Stage, y	Outcome (n/N; Incidence)	Followup Duration, y	Total Ca intake in mg/d	No. of Cases	Total no. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
	≥71 men	HPFS		≥1000	51	nd	1.23	0.67, 2.25		
Park 2009 NIH-AARP[125] [19237724]	50-71, men	Pancreatic cancer (717/293,907; 0.002)	7	526	717 (total)	293,907 (total)	**1 (HR)**	**Reference**	0.39	B
				498			0.93	0.74, 1.16		
				857			0.9	0.72,1.14		
				1073			0.98	0.78, 1.23		
				1530			0.87	0.68, 1.11		
	50-71, women	Pancreatic cancer (384/198,903; 0.002)	7	526	384 (total)	198,903 (total)	**1 (HR)**	**Reference**	0.40	
				498			1.03	0.75, 1.40		
				857			0.93	0.67, 1.28		
				1073			0.97	0.71, 1.34		
				1530			0.88	0.63, 1.24		

Calcium and pregnancy-related outcomes

Preeclampsia.

Synopsis.

This summary is primarily based on a systematic review of 12 RCTs (n=15,528 women) of calcium supplementation (≥1000 mg/d) during pregnancy versus placebo for preventing preeclampsia. In addition, it includes findings from two cohort studies (one of which is a reanalysis of one of the 12 RCTs mentioned above).

Overall, the random effects meta-analysis of the 12 RCTs favored calcium supplementation (RR=0.48, 95 percent CI 0.33, 0.69), albeit with substantial between-study heterogeneity. More than 80 percent of the total number of randomized women (n=12,914) came from two large trials that found no significant effect of calcium supplementation for preventing preeclampsia (RR=0.95, 95 percent CI 0.89, 1.05). Based on their confidence interval, the two large studies excluded large effects of calcium for preeclampsia prevention. There is no obvious explanation for the observed between-study heterogeneity in the aforementioned meta-analysis. The heterogeneity stems from differences in the effects between smaller trials (claiming protective effects) and large trials (showing no effect).

The two cohort studies did not detect associations between calcium intake during the first or second trimester of pregnancy with preeclampsia. Both cohorts were rated B for methodological and reporting quality.

Based on the above, there is not a clear answer to whether calcium supplementation is effective for preeclampsia prevention.

Detailed presentation (Tables 75, 76 & 77).

Relevant published systematic reviews of RCTs (with meta-analyses).

We identified five systematic reviews[173-177] (with meta-analyses) of RCTs on calcium supplementation in the first or second trimester versus placebo for the prevention of preeclampsia (Appendix D). We selected a 2006 Cochrane review as eligible for this section.[176] All other systematic reviews were covered by the Cochrane review. We did not identify any RCTs published after the Cochrane review was conducted.

Eligible were RCTs comparing at least 1000 mg/d of calcium versus placebo in pregnant women. Studies were performed in several countries (both developed and developing). The review defined preeclampsia as high gestational blood pressure (diastolic blood pressure >90 mmHg, or increase more than 15 mm Hg in diastolic or more than 30 mm Hg in systolic blood pressure) with significant proteinuria (at least 300 mg/d or at least 500 mg).[i]

Table 75 summarizes the findings of the Cochrane review. A random effects meta-analysis of all studies suggests that calcium supplementation reduces the risk for preeclampsia (RR=0.48, 95 percent CI 0.33, 0.69). However, there is substantial heterogeneity among the included studies (P<0.001).

i Note that a strict definition of preeclampsia requires confirmation of no hypertension or proteinuria outside of pregnancy.

In subgroup analyses, the effects of calcium appear larger in women at high risk for hypertension versus women at low risk for hypertension. The same is observed when trials are grouped according to whether women had adequate average calcium intake versus low average calcium intake.

More than 80 percent of the total number of randomized women in this meta-analysis (n=12,914) came from two large trials that reported no significant effects of calcium supplementation for preeclampsia (RR=0.95, 95 percent CI 0.89, 1.05; by fixed effects synthesis). Based on their combined confidence interval, these two studies exclude modest and large effects of calcium for preeclampsia prevention. The remaining (smaller) trials show a protective effect. One of the large RCTs was performed in populations with low background calcium diets[178] and the other in populations with adequate background calcium diets.[179]

Allowing for the above, there is no clear explanation for the observed discrepant findings across the trials in the systematic review. The recurrent pattern is that large trials showed no effect for calcium supplementation, whereas smaller trials showed large effects. Calcium supplementation for preeclampsia prevention is a well known example where large trials and smaller trials show systematically different effects. Past methodological explorations (before the publication of the WHO trial[178]) have hypothesized that effects may be observed mostly among women with low calcium in their background diet.[180] However, as mentioned above, this is not supported by the subgroup analyses.

Table 75. Summary table of systematic review on calcium supplementation and preeclampsia, small for gestational age, preterm birth

Author Year [PMID]	Hofmeyr 2006[176] [16855957]
Design (Search Years)	Randomized controlled trials (1988-2006)
Population	Pregnant women less than 35 weeks of gestation regardless of their risk of hypertensive of pregnancy or their previous calcium intake
Intervention (Exposure) and Comparator	Calcium supplement (at least 1000 mg/d) vs. placebo
Results	12 trials (n=15,528)[A] *Preeclampsia (mother):* • All 12 trials (n=15,528): RR=0.48 (0.33, 0.69)[B]; statistically heterogeneous • Among 4 trials (n=5022) with adequate Ca in diet: RR=0.62 (0.32, 1.20); statistically heterogeneous • Among 7 trials (n=10,154) with low Ca in diet: RR=0.36 (0.18, 0.70); statistically heterogeneous • Among 5 trials (n=587) at high risk for hypertension: RR=0.22 (0.12, 0.42); statistically homogeneous • Among 6 trials (n=14,619) at low risk for hypertension: RR=0.68 (0.49, 0.94); statistically heterogeneous *High blood pressure with or without proteinuria (mother):* • Among 11 trials (n=14,946): RR= 0.70 (95% CI 0.57, 0.86); statistically heterogeneous • Among 4 trials (n=5022) with adequate Ca in diet: RR=0.90 (0.81, 0.99); statistically homogeneous • Among 6 trials (n=9684) with low Ca in diet: RR=0.47 (0.29, 0.76); statistically heterogeneous • Among 4 trials (n=327) at high risk for hypertension: RR=0.47 (0.22, 0.97); statistically heterogeneous • Among 7 trials (n=14,619) at low risk for hypertension: RR=0.78 (0.64, 0.95); statistically heterogeneous *Preterm birth:* • Among 10 trials (n=14,751): RR = 0.81 (0.64, 1.03); statistically heterogeneous • Among 4 trials (n=5033) with adequate Ca in diet: RR=0.59 (0.26, 1.33); statistically heterogeneous • Among 6 trials (n=9684) with low Ca in diet: RR=0.90 (0.80, 1.02); statistically homogeneous • Among 4 trials (n=478) at high risk for hypertension: RR=0.45 (0.24, 0.83); statistically homogeneous • Among 7 trials (n=14,183) at low risk for hypertension: RR=0.91 (0.74, 1.12); statistically heterogeneous *Small for gestational age (infant):* • Among 3 trials (n=13,091; fixed effects): RR = 1.10 (0.88, 1.37); statistically homogeneous
Comments	About 80% of participants are from two well designed and well conducted RCTs.[178,179] The two large RCTs show no effects for all four outcomes.

AMSTAR Criteria			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

[A] RR <1.0 favors calcium supplementation
[B] 95% confidence interval

Cohort studies.

We identified two eligible prospective cohort studies (Table 76).[181,182] Both were rated B for methodological and reporting quality. The first was a reanalysis of a large RCT and reported no associations of dietary calcium intakes during the first and second trimester with preeclampsia.[181] The second study was a prospective cohort that again reported no association between dietary calcium intake in the first trimester and risk of preeclampsia.[182] (See Table 77)

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** Not applicable
- **51 – 70 y** Not applicable
- **≥71 y** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Based on a Cochrane review that synthesized data from 12 RCTs on 15,528 pregnant women, calcium supplementation significantly lowered the risk for preeclampsia during pregnancy. However, this meta-analysis was heterogeneous; significant effects were observed only among small studies, and not in the two largest RCTs that comprised more than 80 percent of the women in the meta-analysis. In addition, two cohort studies found no association between calcium intake and preeclampsia. Overall, the effects of calcium supplementation on preeclampsia are unclear.

Table 76. Calcium and preeclampsia and other pregnancy outcomes: Characteristics of cohort studies[A,B]

Author Year Study Name Location (Latitude) [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Outcomes and Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Morris 2007[181] CPEP reanalysis[C] US (various) [11262466]	• Health status • Mean age (SD), y • Male (%)	Healthy ND 0	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles		X	X			X	Total Ca (both)
Oken 2007[182] Project Viva US (42°N) [17521921]	• Health status • Mean age (SD), y • Male (%)	Healthy [most 30 to <40] 0	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome as a function of Ca intake		X	X				Total Ca (both)

[A] Both table entries are treated as cohort studies.
[B] In contrast with most other summary tables of study characteristics, this table is ordered alphabetically by study author.
[C] Reanalysis of the CPEP trial (calcium versus placebo) for preeclampsia prevention focusing on calcium content in diet (and including the intervention dose in the analyses)

Table 77. Calcium and preeclampsia and other pregnancy outcomes: Results of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/d	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Preeclampsia										
Morris 2007[181] CPEP reanalysis US (various) [11262466]	30-40 y, Women	Preeclampsia (326/4314; 7.6%)	ND	579	ND	ND	1.00 (ref)		ND	B
				580-845	ND	ND	0.90	0.61, 1.30		
				846-1131	ND	ND	0.95	0.65, 1.39		
				1132-1560	ND	ND	0.97	0.65, 1.45		
				1561	ND	ND	0.78	0.49, 1.24		
Oken 2007[182] Project Viva US (42°N) [17521921]		Preeclampsia (59/1599; 3.7%)[A]		~1300	59	1599	1.03[B]	0.84, 1.27	NS	B
High blood pressure with or without proteinuria										
Morris 2007[181] CPEP reanalysis US (various) [11262466]	30-40 y, Women	High blood pressure with or without proteinuria (747/4314; 17.3%)	ND	579	ND	ND	1.00 (ref)		ND	B
				580-845	ND	ND	1.09	0.84, 1.42		
				846-1131	ND	ND	1.10	0.83, 1.44		
				1132-1560	ND	ND	1.14	0.85, 1.53		
				1561	ND	ND	1.35	0.98, 1.86		
Oken 2007[182] Project Viva US (42°N) [17521921]		Pregnancy-induced hypertension (119/1659)[C]	ND	~1300	119	1659	0.99	0.85, 1.15	NS	B

[A] Excludes 119 women with pregnancy-induced hypertension – comparison versus normotensive women
[B] Per 300 mg of Ca intake (from supplement or diet)
[C] Excludes 59 women with preeclampsia – comparison versus normotensive women

High blood pressure with or without proteinuria during pregnancy.

Synopsis.

The synopsis of this outcome is based on the same systematic review described under preeclampsia. Overall, the meta-analysis of 11 RCTs favored calcium supplementation RR = 0.70 (95 percent CI 0.57, 0.86) for the treatment of hypertension during pregnancy, with or without proteinuria. However, there was substantial between-study heterogeneity. (Included in this meta-analysis are the two large trials mentioned in the preeclampsia section, which found no significant effect of calcium supplementation on blood pressure.) The systematic review did not offer a clear explanation for the observed heterogeneity.

Based on the above, there is no clear answer to whether calcium supplementation is effective for preventing high blood pressure (with or without proteinuria) in pregnancy.

Detailed presentation (Tables 75, 76 & 77).

Relevant published systematic reviews (with meta-analyses).

The Cochrane review that was selected for preeclampsia was applicable for hypertension during pregnancy[i] as well.[176] Table 75 summarizes the findings of the Cochrane review.

A meta-analysis of 11 trials (14,946 pregnant women) suggested that calcium supplementation reduces the risk for hypertension during pregnancy (RR=0.70, 95 percent CI 0.57, 0.86). However, there is substantial heterogeneity among the included studies ($p<0.001$). As described in Table 75, the heterogeneity was not explained by whether the trials included women with low versus adequate background dietary calcium intake.

In subgroup analyses, the effects of calcium appear larger in women at high risk for hypertension versus women at low risk for hypertension. The same is observed when trials are grouped according to whether women had adequate average dietary calcium intake versus low average calcium intake (see Table 75).

Cohort studies.

A single prospective cohort study[182] (Table 68) reported no association between calcium intake levels and risk for preeclampsia.[182] (See Table 69.)

Findings by life stage.

- **0 – 6 mo** Not applicable
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** Not applicable
- **51 – 70 y** Not applicable
- **≥71 y** Not applicable
- **Postmenopause** Not applicable

[i] The Cochrane review does not clarify whether the women were confirmed normotensive outside pregnancy. This is why we do not use the term pregnancy-induced hypertension for this outcome.

- **Pregnant & lactating women** Based on a Cochrane review that synthesized data from 11 RCTs on 14,946 pregnant women, calcium supplementation significantly lowered the risk for hypertension with or without proteinuria during pregnancy. However, this meta-analysis was very heterogeneous; significant effects were observed only among small studies, and not in the two largest RCTs that comprised more than 80 percent of the women in the meta-analysis. In addition, a cohort study found no association between calcium intake and hypertension during pregnancy. Therefore, the effects of calcium supplementation on hypertension with or without proteinuria during pregnancy are unclear.

Preterm birth.

Synopsis.

The synopsis of this outcome is based on the same systematic review described under preeclampsia. Among 10 RCTs (n=14,751), calcium supplementation has no significant effect on preterm births RR 0.81 (95 percent CI 0.64, 1.03). (Included in this meta-analysis are the two large trials mentioned in the preeclampsia section, which found no significant effects.)

Based on the above, there is no evidence for an effect of calcium supplementation on preterm births.

Detailed presentation (Table 75).

Relevant published systematic reviews (with meta-analyses).

The Cochrane review that was selected for preeclampsia was applicable for preterm birth as well.[176] Table 67 summarizes the findings of the Cochrane review.

A meta-analysis of 10 trials suggests that calcium supplementation had no significant effect on preterm births. There is evidence for between-study heterogeneity in this meta-analysis.

In subgroup analyses, the effects of calcium appear larger in women at high risk for hypertension versus women at low risk for hypertension. The same is observed when trials are grouped according to whether women had low average dietary calcium intake versus adequate average dietary calcium intake.

Findings by life stage.

- **0 – 6 mo** Based on a Cochrane review that synthesized data from ten RCTs on 14,751 pregnant women, calcium supplementation had no significant effect on whether infants were born prematurely or not.
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** Not applicable
- **51 – 70 y** Not applicable
- **≥71 y** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Not applicable

Small for gestational age infant.

Synopsis.

The synopsis of this outcome is based on the same systematic review described under preeclampsia. The overall effects of calcium supplementation were not significant (among three RCTs in 13,091 randomized women RR = 1.10, 95 percent CI 0.88, 1.37). (Included in this meta-analysis are the two large trials mentioned in the preeclampsia section, which found no significant effects.)

Based on the above, there is no evidence for an effect of calcium supplementation on preterm births.

Detailed presentation (Table 75).

Relevant published systematic reviews (with meta-analyses).

The Cochrane review that was selected for preeclampsia was applicable for this outcome as well.[176] Table 75 shows that among three trials with pertinent information there was no significant effect of calcium supplementation on the proportion of infants who were small for gestational age.[178,179]

Findings by life stage.

- **0 – 6 mo** Based on a Cochrane review that synthesized data from three RCTs on 13,091 pregnant women, calcium supplementation has no significant effect on whether born infants were small for gestational age or not.
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** Not applicable
- **51 – 70 y** Not applicable
- **≥71 y** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Not applicable

Calcium and all-cause Mortality

Synopsis.

One cohort study (rated B for methodological and reporting quality) reported no significant associations between calcium intakes and all-cause mortality in men or women aged between 40-65 years. No RCTs of calcium intake evaluated all-cause mortality.

Detailed presentation (Tables 78 & 79).

One cohort study from Amsterdam, Netherlands (52°N), reported in two publications[105,126] evaluated associations between calcium intake and all-cause mortality. The cohort was based on a general population health survey and enrolled civil servants or their spouses (aged 40-65 years). The reports received grade "B" for methodological and reporting quality (Table 70).

The publications reported no association between calcium intake and all-cause mortality among men or women. Table 71 shows the results of the various analyses conducted in the two publications.[105,126]

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** One cohort study found no associations between calcium intakes and all-cause mortality in men or women aged between 40-65 y.
- **51 – 70 y** The above (19-50 y) may be applicable here as well, based on the age range of cohort participants.
- **≥71 y** No data
- **Postmenopause** No data
- **Pregnant & lactating women** No data

Table 78. Calcium intake and all-cause mortality: Characteristics of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Population		Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Van der Vijver 1992[105] & Slob 1993[126] Netherlands (52°N) [1544755 & 8478144]	• Health status • Age range, y • Male (%)	General population 40-65y 51	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Outcome stratified by total Ca intake quintiles	X	X	X			X	Total Ca (food)

Table 79. Calcium intake and all-cause mortality: Results of cohort studies

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration	Total Ca Intake, mg/d	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Van der Vijver 1992[105] & Slob 1993[126] Netherlands (52°N) [1544755 & 8478144]	40-65 y, men	All cause mortality (nd)	336 mo (28 y)	≤585	nd	nd	1.1	0.7, 1.6	nd	B
				585 - 725	nd	nd	1.1	0.7, 1.6		
				725 - 935	nd	nd	0.8	0.5, 1.2		
				935 - 1245	nd	nd	0.9	0.6, 1.3		
				>1245	nd	nd	**1.0**	**Reference**		
Van der Vijver 1992[105] & Slob 1993[126] Netherlands (52°N) [1544755 & 8478144]	40-65 y, women	All cause mortality (nd)	336 mo (28 y)	≤445	nd	nd	1.2	0.8, 1.9	nd	B
				445 - 540	nd	nd	1.1	0.7, 1.7		
				540 - 640	nd	nd	1.3	0.9, 2.0		
				640 - 850	nd	nd	1.1	0.7, 1.7		
				>850	nd	nd	**1.0**	**Reference**		

Calcium and Hypertension and Blood Pressure

We searched for systematic reviews and primary studies that evaluated associations between calcium intake or body stores and incidence of hypertension and change in blood pressure. For the outcome *incidence of hypertension*, we reviewed randomized controlled trials and other longitudinal studies. For the outcome *change in blood pressure*, we reviewed only randomized controlled trials. The EPC and the TEP agreed that due to the large volume of literature, the limited resources would not be expended on reviewing observational studies for the surrogate outcome blood pressure. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the pregnancy section.

Calcium and hypertension.

Synopsis.

No systematic reviews evaluated the association between calcium intake and incidence of hypertension. The association has been analyzed in five large studies (6 articles/analyses). No RCTs of calcium intake evaluated hypertension incidence. In analyses of men and women together and of men alone, there was no evidence of an association between calcium intake and risk of hypertension. In the Women's Health Study (WHS), a highly significant trend was found across quintiles of calcium intake and risk of hypertension, with significantly lower rates of hypertension found among women consuming at least 679 mg calcium per day compared to less than 558 mg calcium per day. The two articles that reported subgroup analyses based on age found associations between lower calcium intake and hypertension among younger adults (below 40 or 50 years of age), but no significant associations in older adults.

Detailed presentation (Tables 80 & 81 and Figure 21).

The six articles, reporting investigations of five studies, included two analyses of combined men and women in the NHANES I study and Navarra, Spain (both methodological quality C),[183,184] two analyses of men alone in the Health Professionals Follow-up Study (HPFS) and NHANES I (of methodological quality B and C, respectively), [185,186] and three analyses of women alone in the WHS, the Nurses Health Study (NHS), and NHANES I (of methodological quality A, B, and C, respectively).[186-188] All studies included only people without hypertension at baseline. Only the A quality analysis, WHS, included elevated blood pressure in their outcome definition of hypertension; all other analyses used self-reported hypertension (generally based on a physician's diagnosis or treatment). The mean ages of the participants varied widely across studies (36-54 years) among those that reported mean data; the range of ages within studies varied from broad (20-90 years) to narrow (30-55 years) among those that reported ranges. All studies reported adjusted analyses; though each adjusted for different factors. Most of the studies were limited by such factors as reliance on self-reported hypertension (without assessment of blood pressure), exclusion of numerous participants due to lack of data, inadequate reporting of results data, and lack of reporting of definitions (ranges or averages of calcium quintiles).

Two studies reported analyses for combined men and women. These are discussed here. The remaining analyses of men or women separately are discussed below. In analyses of combined men and women (each with almost 7000 participants), neither study reported a significant association. No significant trend or individual analyses of quintiles was found in the short duration (2 years) Spanish cohort study. A poorly reported analysis from NHANES I concluded that there was progressively higher incidence of hypertension in lower quartiles of calcium

intake after 10 years, but no statistical analysis was performed and the definitions of the quartiles were not provided.

Findings per calcium intake level.

Among the studies that provided definitions of the compared categories of calcium intake, consistent significant associations were found for calcium intakes below 500 mg/day in men under age 50 years (compared to over 1100 mg/day) and below 558 mg/day in women (compared to over 678 mg/day).

Findings per age and sex.

Men alone were analyzed from the PHFS (about 31,000 men) and NHANES I (about 2000 men, split by race). Neither analysis found a significant trend or any significant differences among different calcium intake categories at 4 and 10 years, respectively for the two studies.

Women alone were analyzed from three studies. The studies had heterogeneous findings. The A quality analysis of the WHS (about 29,000 women) found a highly significant trend across quintiles ($P<0.0001$) at 10 years with a significantly higher rate of hypertension in women in the lowest calcium intake quintile (189-557 mg/day) compared to all quintiles with intakes above 679 mg/day. However, the B quality analysis of the NHS (about 41,500 women) found no significant association by calcium intake at 14 years and the C quality analysis of NHANES I (about 3500 women, split by race) found no consistent association at 10 years.

One C quality analysis of NHANES I assessed subgroups of combined men and women by age (divided at 40 years old). Among people under age 40 years, those in the lowest quartile of calcium intake had significantly higher rates of being treated for hypertension after 10 years; however, the article failed to define the calcium intake quartiles. No significant association was found among older participants. In the HPFS, in men under age 50 years, a higher rate of hypertension at 4 years was found in those with calcium intake less than 500 mg/d compared to over 1100 mg/d; but no association was found in older men.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** Five of the six studies included mostly people within this life stage.[183-186,188] Overall, there was no evidence of a significant association between calcium intake and risk of hypertension. However, as described in detail in the Findings per age and sex section above, in two subgroup analyses, significant associations were found between the lowest category of calcium intake and increased risk of hypertension in younger people (under age 40 – calcium intake range not reported, or age 50 years – less than 500 mg/d compared to over 1100 mg/d.
- **51 – 70 y** Four of the six studies included people largely within this life stage.[184,185,187,188] The studies mostly found no significant associations between calcium intake and risk of hypertension, including within the 2 subgroups of adults above 40 or 50 years of age. However, the WHS, which included women mostly within this life stage, found a highly significant trend across quintiles ($P<0.0001$) at 10 years with a significantly higher rate of hypertension in women in the lowest calcium intake quintile (189-557 mg/d) compared to all quintiles with intakes above 679 mg/d.

- **≥71 y** Few of the people in the studies appear to have been in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Postmenopause** Only the WHS appeared to have included (or analyzed) primarily postmenopausal women. The study found a highly significant trend across quintiles ($P<0.0001$) at 10 years with a significantly higher rate of hypertension in women in the lowest calcium intake quintile (189-557 mg/d) compared to all quintiles with intakes above 679 mg/d.
- **Pregnant & lactating women** Not reviewed

Table 80. Calcium and hypertension incidence: Characteristics of cohort studies

Author Year Study Name Location [PMID]	Population		Dietary Calcium intake		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV exposure	Lifestyle	
Alonso 2005[183] U Navarra Follow-up Navarra Spain (43°N) [16280427]	• Health status • Mean age (range), y • Male (%)	Normo-tensive 36 (20-90) 39	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Hypertension incidence stratified by total Ca intake quintiles	X	X	X	X		X	Total Ca (both)
Dwyer 1996[184A] NHANES I US (various) [8890661]	• Health status • Mean age (range), y • Male (%)	Normo-tensive 46 (25-74) 63	• Dietary assessment method • Internal validation? (y/n)	24 hr recall nd	Hypertension incidence stratified by total Ca intake quartiles	X	X	X			X	Total Ca (both)
Ascherio 1992[185] HPFS US (various) [1330360]	• Health status • Median age (range), y • Male (%)	Normo-tensive 50 (40-75) 100	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Hypertension incidence stratified by total Ca intake categories		X	X			X	Total Ca (both)
Ford 1991[186B] NHANES I US (various) [1937662]	• Health status • Mean age (range), y • Male (%)	Normo-tensive nd (≥25) 35	• Dietary assessment method • Internal validation? (y/n)	nd nd	Hypertension incidence stratified by total Ca intake quartiles	X	X					Total Ca (both)
Wang 2008[187] WHS US (various) [18259007]	• Health status • Mean age (SD, range), y • Male (%)	Normo-tensive 54 (6.5; ≥45) 0	• Dietary assessment method • Internal validation? (y/n)	FFQ No	Hypertension incidence stratified by total Ca intake quintiles	X	X	X	X		X	Total Ca (both)
Ascherio 1996[188] NHS US (various) [8621198]	• Health status • Mean age (range), y • Male (%)	Normo-tensive nd (30-55) 0	• Dietary assessment method • Internal validation? (y/n)	FFQ Yes	Hypertension incidence stratified by total Ca intake categories		X	X			X	Total Ca (both)

[A] Overall and age subgroup analyses from NHANES I reported in this study. However, different samples selected; 63% male.
[B] Sex and race subgroup analyses from NHANES I reported in this study. However, different samples selected; 35% male.

Table 81. Calcium and hypertension incidence: Results of cohort studies

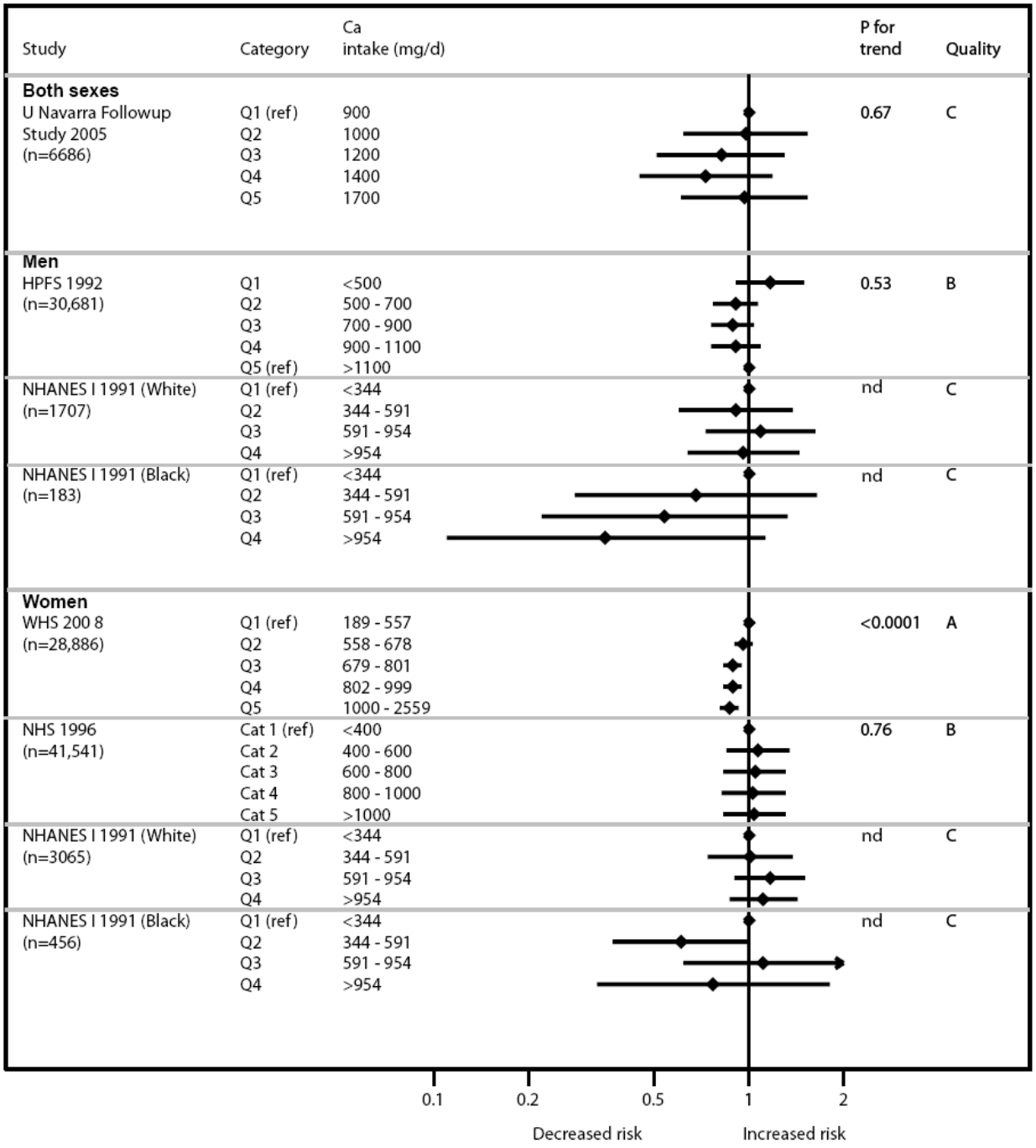
Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N, Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Both Sexes										
Alonso 2005[183] U Navarra Follow-up [16280427]	20-90 y, Both	Hypertension (180/6686, 0.027)	2 y	Mean (SD) **900 (200)**	39	~1337	**1**	**Reference**	0.67	C
				1000 (200)	39	~1337	0.98	0.62, 1.54		
				1200 (200)	35	~1337	0.82	0.51, 1.30		
				1400 (300)	30	~1337	0.73	0.45, 1.19		
				1700 (400)	37	~1337	0.97	0.61, 1.54		
Dwyer 1996[184A] NHANES I [8890661]	25-74 y, Both	Hypertension, treated (1704/6634, 0.257)	10 y	nd	nd	~1658	29.8%		nd	C
				nd	nd	~1658	~27%			
				nd	nd	~1658	~25%			
				nd	nd	~1658	21.3%			
	≤40 y	Hypertension, treated (nd/nd)	10 y	**nd**	nd	nd	**1**	**Reference**		
				nd	nd	nd	0.70	0.54, 0.91[C]	nd	
				nd	nd	nd	0.79	0.66, 0.94[C]		
				nd	nd	nd	0.89	0.81, 0.97[C]		
	>40 y	Hypertension, treated (nd/nd)	10 y	**nd**	nd	nd	**1**	**Reference**		
				nd	nd	nd	1.01	0.94, 1.08	nd	
				nd	nd	nd	1.02	0.89, 1.18		
				nd	nd	nd	1.04	0.84, 1.28		
Men										
Ascherio 1992[185] HPFS [1330360]	40-75 y, Men	Hypertension (1248/30,681, 0.041)	4 y	<500	85	1677	1.17	0.91, 1.50	0.53	B
				500-700	297	7504	0.91	0.77, 1.07		
				700-900	333	8576	0.89	0.76, 1.04		
				900-1100	195	5038	0.91	0.76, 1.09		
				≥1100	338	7890	**1**	**Reference**		
	≤50 y	Hypertension (nd/14,354)	4 y	<500	nd	nd	1.52	nd*	nd	
				500-1100	nd	nd	0.86	nd		
				≥1100	nd	nd	**1**	**Reference**		
	>50 y	Hypertension (nd/16,314)	4 y	<500	nd	nd	0.98	nd		
				500-1100	nd	nd	0.91	nd		
				≥1100	nd	nd	**1**	**Reference**		

continued

Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N, Incidence)	Followup Duration (Time to Dx)	Total Ca Intake, mg/day	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Ford 1991[186B] NHANES I [937662]	≥25 y, Men (White)	Hypertension (360/1707, 0.211)	10 y	<344	47	~215	**1**	**Reference**	nd	C
				344-591	78	~382	0.91	0.60, 1.38		
				591-954	104	~448	1.09	0.73, 1.63		
				>954	131	~662	0.96	0.64, 1.45		
	≥25 y, Men (Black)	Hypertension (64/183, 0.350)	10 y	<344	20	~34	**1**	**Reference**	nd	
				344-591	17	~45	0.68	0.28, 1.65		
				591-954	18	~56	0.54	0.22, 1.33		
				>954	9	~34	0.35	0.11, 1.13		
Women										
Wang 2008[187] WHS [8259007]	≥45 y, Women	Hypertension (8529/28,886, 0.295)	10 y	**189-557**	1860	5777	**1**	**Reference**	<0.0001	A
				558-678	1778	5777	0.96	0.90, 1.03		
				679-801	1626	5777	0.89	0.83, 0.95[C]		
				802-999	1634	5777	0.89	0.83, 0.95[C]		
				1000-2559	1631	5777	0.87	0.81, 0.93[C]		
Ascherio 1996[188] NHS [621198]	30-55 y, Women	Hypertension (2526/41,541, 0.061)	14 y	**<400**	87	5581 person-y	**1**	**Reference**	0.76	B
				400-600	608	36,605	1.07	0.85, 1.35		
				600-800	712	42,544	1.05	0.83, 1.31		
				800-1000	407	24,240	1.03	0.82, 1.31		
				≥1000	712	41,325	1.04	0.83, 1.31		
Ford 1991[186B] NHANES I [937662]	≥25 y, Women (White)	Hypertension (645/3065, 0.210)	10 y	<344	186	~865	**1**	**Reference**	nd	C
				344-591	183	~806	1.11	0.87, 1.43		
				591-954	172	~775	1.17	0.90, 1.51		
				>954	104	~619	1.01	0.74, 1.38		
	≥25 y, Women (Black)	Hypertension (171/456, 0.375)	10 y	<344	94	~225	**1**	**Reference**	nd	
				344-591	35	~120	0.61	0.37, 1.01		
				591-954	31	~74	1.11	0.62, 2.01		
				>954	11	~37	0.77	0.33, 1.81		

* Statistically significant (P<0.05)
[A] Overall and age subgroup analyses from NHANES I reported in this study. However, different samples selected; 63% male.
[B] Sex and race subgroup analyses from NHANES I reported in this study. However, different samples selected; 35% male.
[C] Estimated from available data

Figure 21. Hypertension risk stratified by calcium intake



Calcium and blood pressure.

Synopsis.

We identified six systematic reviews that evaluated RCTs of calcium intake and changes in blood pressure. Five additional trials not identified by these systematic reviews met eligibility criteria for this report and are summarized together with the systematic reviews. Altogether, 69 trials have been identified. The range of intervention calcium doses were approximately 400 to 2000 mg/d, with most studies using 1000 to 1500 mg/d. The systematic reviews followed the patterns of the primary studies in that they were divided among those that focused on studies of people without hypertension, people with hypertension, and general populations (with or without hypertension, without subgroup analyses). Because the systematic reviews all used somewhat different eligibility criteria, they included overlapping groups of trials. No one or two systematic reviews captured most of the relevant trials; therefore, all systematic reviews are included here.

Two overlapping systematic reviews evaluated trials of normotensive individuals. Both found no significant effect of calcium supplementation and blood pressure. The two additional, more recent primary studies of normotensive participants were consistent with this finding.

Four overlapping systematic reviews of the effect of calcium on blood pressure in hypertensive individuals mostly found significant effects on systolic blood pressure (ranging from about -2 to -4 mm Hg). An older, highly selective systematic review found no significant effect. The systematic review that found the largest effect of calcium on systolic blood pressure also found a significant effect on diastolic blood pressure (-1.5 mm Hg), but the other systematic reviews found no significant effect. None of the more recent primary studies were in people exclusively with hypertension.

Four of the systematic reviews performed meta-analyses of all people regardless of hypertension diagnosis. Except for the oldest, highly selective systematic review, they found significant effects on systolic blood pressure (ranging from -1.9 to –0.9 mm Hg). The summary estimates of the effect on diastolic blood pressure ranged from -1.0 to +0.03 mm Hg, which were mostly nonsignificant. The individual, recent primary studies of mixed populations (in terms of hypertension) found larger, though statistically nonsignificant, effects.

The systematic reviews that evaluated factors including age, sex, calcium dose, background dietary calcium, supplement versus dietary source, and other factors found no significant associations (or differences). The five additional primary studies did not provide further insights into these subgroup analyses.

Detailed presentation (Tables 82, 83, & 84).

The six systematic reviews explicitly or implicitly used generally different eligibility criteria, resulting in large overlaps in the trials included.[169,189-193]. The systematic reviews included a total of 64 trials. The largest systematic review[189] included trials up to 1997 and was an update of a previous review[191] that reported more analyses. The next largest systematic review[190] was one of the more recent systematic reviews (including trials through 2003). The most recent systematic review[169] was restricted to trials of people with hypertension. Five more recent trials, not included in any of the systematic reviews were found.[120,194-197] Two of the trials were restricted to normotensive individuals; none included only people with hypertension.

Normotensive individuals.

The systematic reviews by Bucher et al. (1996)[191] and Allender et al. (1996)[192] evaluated trials of normotensive individuals. The range of intervention calcium doses were approximately 400 to 2000 mg/d, with most studies using 1000 to 1500 mg/d. Both found no significant effect of calcium supplementation on blood pressure (net effect on systolic blood pressure of -0.27 and -0.53 mm Hg, respectively, and on diastolic blood pressure of -0.33 and -0.28 mm Hg, respectively). The two additional, more recent primary studies of normotensive participants were consistent with this finding. The TOHP trial compared calcium supplement to placebo in people without hypertension but high normal diastolic blood pressure (80-89 mm Hg) and found a nonsignificant net change in blood pressure of approximately -0.5/+0.35 mm Hg (systolic/diastolic) after 18 months.[195] Lijnen 1995 also compared calcium supplement to placebo, but in men who had been put on a low calcium run-in diet, and found a nonsignificant net change in blood pressure of approximately -2/-1 mm Hg after 4 months.[197] Both trials had methodological quality C due to inadequate reporting of this outcome or of the background calcium intakes of the participants. Bucher et al. (1996) reported a wide range of study quality; Allender et al. (1996) did not evaluate study quality.

Findings per calcium intake level.

Neither systematic review performed subgroup analyses of the normotensive individuals to evaluate a dose (calcium intake) effect. Qualitative examination of the data provided in the systematic review tables and the two additional trials did not indicate any dose effect.

Findings per age and sex.

Neither systematic review performed subgroup analyses of the normotensive individuals to evaluate age or sex. The trials in the Allender et al. (1996) systematic review and the two additional trials represented a wide range of ages, though apparently all participants were under age 70 years. Studies were of all men, all women, and both sexes. There were no apparent differences based on age or sex.

Hypertensive individuals.

Four systematic reviews evaluated trials of hypertensive individuals (Bucher et al. 1996[191], Allender et al. 1996[192], Cappuccio et al. 1989[193], and Dickinson 2006[198]). Dickinson et al. (2006) included only studies of people with hypertension. The range of supplemental calcium was approximately 400 to 2000 mg/d in most systematic reviews, with most studies using 1000 to 1500 mg/d. The systematic reviews generally found significant effects on systolic blood pressure of about -2 to -4 mm Hg, but no (or small) effects on diastolic blood pressure. The one systematic review that found no effect of calcium supplementation on systolic blood pressure (Cappuccio et al. 1989) was the oldest systematic review (including trials up to only 1988). In addition, the reviewers were highly selective in their eligibility criteria, having excluded trials that did not report various types of baseline data. The one systematic review that found a significant effect of calcium supplementation on diastolic blood pressure (Bucher et al. 1996) meta-analyzed only 6 trial subgroups of people with hypertension, compared to 10 to 16 trials in the other systematic reviews. None of the more recent trials provided analyses in only people with hypertension.

Findings per calcium intake level.

Only Dickinson et al. (2006), the systematic review of only trials of people with hypertension, evaluated calcium intake (or dose) as a predictor of effect. They found essentially the same overall effects on systolic and diastolic blood pressures in studies that used less than 1200 mg/d or 1200 to 2000 mg/d of calcium. Qualitative examination of the data provided in the tables of the remaining systematic reviews did not indicate any dose effect.

Findings per age and sex.

No systematic review evaluated the association between age or sex and treatment effect in trials of people with hypertension. Overall, the range of ages of participants was about 20 to 75 years. Studies were of all men, all women, and both sexes. There were no apparent differences based on age or sex.

All trials (combined normotensive and hypertensive individuals).

Five systematic reviews (including one which is an update of a second) combined trials of hypertensive, normotensive, or mixed groups of people (Griffith et al. 1999[189], van Mierlo et al. 2006[190], Bucher et al. 1996[191], Allender et al. 1996[192], and Cappuccio et al. 1989[193]). The range of calcium supplementation was approximately 400 to 2000 mg/d in most systematic reviews, with most studies using 1000 to 1500 mg/d. The systematic reviews generally found a significant effect of calcium supplementation on systolic blood pressure of -0.9 to -1.9 mm Hg (excluding the earliest, highly selective systematic review by Cappuccio et al. (1989)[193], as discussed above). The two systematic reviews that included the most studies (Griffith et al. 1999[189] and van Mierlo et al. 2006[190]) found a significant effect on diastolic blood pressure (-0.8 and -1.0 mm Hg, respectively). The smaller, older systematic reviews found no significant effect (Allender et al. 1996[192] and Cappuccio et al. 1989[193]). The reason for the difference in conclusions of the systematic reviews may relate to greater statistical power in the more recent meta-analyses or differences in study eligibility criteria. The systematic reviews that reported on study heterogeneity found significant heterogeneity. Three of the systematic reviews reported data on subgroup or regression analyses to explain the heterogeneity. The only factor that explained a significant amount of the heterogeneity was the difference in effect between studies of people with or without hypertension. (The age, sex, and calcium dose analyses are described below.)

Two recent randomized trials included postmenopausal women (over 50 or 55 years) regardless of their blood pressure;[120,194] a third trial enrolled pregnant women and evaluated long-term postpartum blood pressures.[196] The trials each compared different interventions: calcium citrate 1000 mg versus placebo; dairy product intake (with a mean of 1242 mg/d calcium) versus nondairy product intake (377 mg/d calcium); and calcium carbonate 2000 mg/d versus placebo in women all taking prenatal vitamins that included 400 IU/d vitamin D_2. The calcium citrate trial was of methodological quality B; the other two trials C. The recent trials found broadly similar conclusions to that of the systematic reviews, with women with greater calcium intake having lower systolic blood pressure (-2.2 to -5.4 mm Hg) and smaller decreases in diastolic blood pressure (-0.7 to -2.2 mm Hg); though none of the effects was statistically significant.

Findings per calcium intake.

Three systematic reviews[190-192] evaluated calcium dose (or intake) as a source of heterogeneity. None found a significant association. Specifically, van Mierlo et al. (2006) found similar (though smaller) effects in studies of over 1000 mg/d of calcium (SBP/DBP -1.75/-0.56) compared to studies of 1000 mg/d of calcium or less (-2.17/-1.41).

Findings per age and sex.

Age and sex were evaluated as potential explanations of heterogeneity in two systematic reviews.[190,192] Neither found that age or sex were significantly associated with the effect of calcium on blood pressure. However, these analyses are subject to ecological fallacy, as they used the mean ages and the percent of study participants who were male as proxies for the effects of calcium intake in people of a particular age or sex. Most studies included participants under age 70 years. Studies were of all men, all women, and both sexes.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The majority of studies are applicable to people within this life stage; though people under approximately 40 years are less well represented. The evidence suggests no significant effect of calcium supplementation on blood pressure in normotensive individuals. In people with hypertension, the evidence suggests that calcium supplementation lowers systolic blood pressure by about -2 to -4 mm Hg, but does not change diastolic blood pressure. The effect appears to be consistent across calcium supplement doses (specifically above or below 1200 mg/d).
- **51 – 70 y** The majority of studies are applicable to people within this life stage. The conclusions are the same as for those in the 19-50 years life stage.
- **≥71 y** The evidence is scant for this life stage. Few of the studies appear to have included people over age 70 years.
- **Postmenopause** Our review of the evidence does not allow for a definitive conclusion for this life stage. None of the systematic reviews evaluated menopausal status as an explanatory variable for heterogeneity.
- **Pregnant & lactating women** Not reviewed

Table 82. Summary of systematic reviews of calcium and blood pressure

Author Year [PMID]	Griffith 1999[189] [10075392]
Design (Search Years)	Randomized controlled trials (1966-1997)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 600-2000 mg (36% 1000 mg; 26% 1500-1600 mg; 12% 2000 mg)
Results	42 trials SBP: -1.44 (-2.20, -0.68)[A]; statistically heterogeneous DBP: -0.84 (-1.44, -0.24); statistically heterogeneous Subgroup analyses did not find that heterogeneity could be explained by age, sex, baseline calcium, dietary versus nondietary calcium, or quality. Subgroups with hypertensive versus normotensive people were significantly different (no further details). Conclusions similar to previous systematic review (Bucher 1996[191])
Comments	Update of Bucher 1996[191] (see below).

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Study quality not discussed in conclusions. Funding source reported, but not conflict of interest.	

Author Year [PMID]	van Mierlo 2006[190] [16673011]			
Design (Search Years)	Randomized controlled trials (1966-2003)			
Population	Both hypertensive and normotensive participants			
Intervention and Comparator	Calcium supplementation versus placebo (no supplement) Dose range 355-2000 mg (40% 1000 mg; 32% 1500-1600 mg; 6% 2000 mg)			
Results	40 trials SBP: -1.86 (95% CI -2.91, -0.81); statistically heterogeneous DBP: -0.99 (95% CI -1.61, -0.37); statistically heterogeneous In multivariable analysis including age, sex, initial calcium intake, calcium dose, and initial blood pressure:			
			SBP	DBP
	Age	<45 y	-1.45 (-2.99, +0.09)	-1.26 (-2.20, -0.33)
		≥45 y	-2.33 (-3.69, -0.96)	-0.80 (-1.62, +0.02)
	Male	≤50%	-2.20 (-3.68, -0.72)	-1.12 (-1.98, -0.26)
		>50%	-1.77 (-3.13, -0.42)	-0.84 (-1.65, -0.04)
	Initial BP	<140/90 mm Hg	-2.04 (-3.40, -0.68)	-1.04 (-1.86, -0.22)
		≥140/90 mm Hg	-1.85 (-3.45, -0.32)	-0.89 (-1.79, +0.01)
	Ca dose	≤1000 mg	-2.17 (-3.59, -0.75)	-1.41 (-2.24, -0.59)
		>1000 mg	-1.75 (-3.20, -0.31)	-0.56 (-1.40, +0.29)
	Blood pressures not statistically significantly different between any strata.			
Comments				

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Unclear	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Partial	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	No data on inclusion of unpublished data. Excluded studies available from authors	

Table 82. continued

Author Year [PMID]	Bucher 1996[191] [8596234]
Design (Search Years)	Randomized controlled trials (1966-1994)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation vs. placebo (no supplement) Dose range 406-2000 mg (41% 1000 mg; 31% 1500-1600 mg; 8% 2000 mg)
Results	33 trials [Overall summary results were updated in Griffith 1999[189], above] Studies with specified subgroups of hypertensive and normotensive participants (6 trials): Hypertensives SBP -4.30 (-6.47, -2.13) DBP -1.50 (-2.77, -0.23) Normotensives SBP -0.27 (-1.80, +1.27) DBP -0.33 (-1.56, +0.90) Regression analyses: BP (continuous scale) SBP OR = 0.99 (0.96, 1.01) DBP OR = 0.99 (0.96, 1.03) Dose of calcium, duration of supplementation, dietary vs. nondietary calcium supplementation, methodological quality did not demonstrate a relationship with the magnitude of treatment effect.
Comments	Updated in Griffith 1999[189] (see above)

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Funding source reported, but not conflict of interest.	

Author Year [PMID]	Allender 1996[192] [8610952]
Design (Search Years)	Randomized controlled trials (1982-1993)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation vs. placebo (no supplement) Dose range 400-2160 mg (35% 1000 mg; 29% 1500-1600 mg; 10% 2000 mg)
Results	26 trials (22 trials included in meta-analyses) SBP: -0.89 (-1.74, -0.05) DBP: -0.18 (-0.75, +0.40) Hypertensives SBP -1.68 (-3.18, -0.18) DBP +0.02 (-0.96, +1.00) Normotensives SBP -0.53 (-1.56, +0.49) DBP -0.28 (-0.99, +0.42) By weighted linear regression analyses, age, sex, calcium dose, trial duration were not associated with treatment effect (P>0.10)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Author Year [PMID]	Cappuccio 1989[193] [2697729]
Design (Search Years)	Randomized controlled trials (1983-1988)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Nondietary calcium supplementation versus placebo (no supplement) or low calcium intake Dose range 800-1600 mg (60% 1000 mg; 27% 1500-1600 mg)
Results	15 trials SBP (supine): -0.13 (-0.46, +0.19) DBP (supine): +0.03 (-0.17, +0.22) Hypertensives SBP +0.06 (-0.59, +0.72) DBP +0.03 (-0.21, +0.27)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	nd	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Table 82. continued

Author Year [PMID]	Dickinson 2006[198] [16625609][B]
Design (Search Years)	Randomized controlled trials (1982-2003/2005[C])
Population	Hypertensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2000 mg (50% 1000 mg; 25% 1500-1600 mg; 6% 2000 mg)
Results	13 trials SBP: -2.53 (-4.45, -0.60); statistically heterogeneous DBP: -0.81 (-2.07, +0.44); statistically heterogeneous Ca dose <1200 mg SBP -2.67 (-5.15, -0.18) DBP -0.75 (-2.13, +0.63) Ca dose 1200-2000 mg SBP -2.69 (-5.86, +0.47) DBP -0.78 (-3.82, +2.25) Not statistically significantly different by calcium dose
Comments	

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

[A] Numbers in parentheses are 95% confidence intervals
[B] A technical update, with no further studies added was published in the Cochrane database in 2008.
[C] Different dates for different databases.

Table 83. Calcium and blood pressure: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Whelton 1997[195] TOHP US (various) [9022561]	• Health status • Mean age (range), y • Male (%)	No HTN (DBP 80-89 mm Hg) 43 (30-54) 68	nd	Calcium supplement vs. Placebo	nd	
Lijnen 1995[197] Leuven, Belgium (51°N) [8557965]	• Health status • Mean age (range), y • Male (%)	Normotensive 24 (20-44) 100	"Low calcium diet" run-in	Calcium supplement vs. Placebo	nd	With low dairy intake
Reid 2005[194] Auckland, New Zealand (36.5°S) [15827103]	• Health status • Mean age (range), y • Male (%)	Healthy 75 (≥55) 0	Ca 857 mg/day	Calcium supplement vs. Placebo	Calcium group: 55%, Placebo group: 58%	
Ghadirian 1995[120] Montreal, Canada (46°N) [7493659]	• Health status • Mean age (range), y • Male (%)	Healthy ~80 (≥50) 0	Ca 776 mg/day	Dairy vs. Dairy-free intake	Non-compliant and those who provided incomplete data were excluded.	
Hatton 2003[196] CPEP Portland, Oregon (45.5°N) [14553957]	• Health status • Mean age (range/SD), y • Male (%)	Pregnant during trial nd 0	nd	Calcium supplement vs. Placebo (both on prenatal vitamins including Vit D_2 400 IU)	nd (but all had to meet a compliance test prior to randomization)	Oregon site only. Post-pregnancy followup

Table 84. Calcium and blood pressure: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex; Population	Outcome	1°/2°	Mean Followup, unit	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Normotensive														
Whelton 1997[195] TOHP [9022561]	30-54 y, Both; No HTN (DBP 80-89 mm Hg)	SBP	1°	18 mo	Ca carbonate 1000 mg	221	mm Hg	126.0	nd	nd	~-0.5[A]	~-2, -1	NS	C
					Placebo	224		125.4	nd	nd				
Lijnen 1995[197] Belgium [8557965]	20-44 y, Men No HTN	SBP, supine	2°	4 mo	Ca gluconate 2000 mg (low dairy intake)	16	mm Hg	114	~-4[A]	nd	~-2	nd	NS	C
					Placebo (low dairy intake)	16		114	~-2	nd				
All women														
Reid 2005[194] New Zealand [15827103]	≥55 y, Women; All BP	SBP	2°	30 mo	Ca citrate 1000 mg	732	mm Hg	134.9	0.0	-0.1, 0.1	-2.4	-0.8, 5.6	0.14	B
					Placebo	739		133.9	+2.4	2.3, 2.5				
Ghadirian 1995[120] Canada [7493659]	≥50 y, Women; All BP	SBP	2°	1 mo	Dairy intake (1242 mg Ca)	81	mm Hg	140.34	-2.69	-7.3, 2.0*	-5.4	-12.3, 1.4[C]	NS	C
					Dairy-free (377 mg Ca)	77		131.71	+2.75	-2.3, 7.8*				
Hatton 2003[196] CPEP [14553957]	Pregnant, Women[B]; All BP	SBP	2°	2 y post-partum	Ca carbonate 2000 mg (+Vit D_2 400 IU)	37	mm Hg	nd		Final 101.9	Difference -2.2	-7.8, 3.4[C]	NS	C
					Placebo (+Vit D_2 400 IU)	25		nd		104.1				
DIASTOLIC BLOOD PRESSURE														
Normotensive														
Whelton 1997[195] TOHP [9022561]	30-54 y, Both; No HTN (DBP 80-89 mm Hg)	DBP	1°	18 mo	Ca carbonate 1000 mg	221	mm Hg	84.1	nd	nd	~+0.35[A]	~-1, 1	NS	C
					Placebo	224		83.9	nd	nd				
Lijnen 1995[197] Belgium [8557965]	20-44 y, Men No HTN	DBP, supine	2°	4 mo	Ca gluconate 2000 mg (low dairy intake)	16	mm Hg	74	~-1[A]	nd	~-1	nd	NS	C
					Placebo (low dairy intake)	16		72	~0	nd				
All women														
Reid 2005[194] New Zealand [15827103]	≥55 y, Women; All BP	DBP	2°	30 mo	Ca citrate 1000 mg	732	mm Hg	70.1	-0.2	-0.2, -0.2	-1.0	-2.3, 0.3	0.13	B
					Placebo	739		69.6	+0.8	0.8, 0.8				

continued

Author Year Study Name [PMID]	Age Range, Sex; Population	Outcome	1°/2°	Mean Followup, unit	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Ghadirian 1995[120] Canada [7493659]	≥50 y, Women; All BP	DBP	2°	1 mo	Dairy intake (1242 mg Ca)	81	mm Hg	81.17	-7.78	-10.0, -5.5*	-2.2	-5.4, 1.0[C]	NS	C
					Dairy-free (377 mg Ca)	77		79.09	-5.59	-7.9, -3.3*				
Hatton 2003[196] CPEP [14553957]	Pregnant, Women[B]; All BP	DBP	2°	2 y post-partum	Ca carbonate 2000 mg (+Vit D_2 400 IU)	37	mm Hg	nd		Final 67.1	Difference -0.7	-4.8, 3.4	NS	C
					Placebo (+Vit D_2 400 IU)	25		nd		67.8				

[A] From figure
[B] Blood pressure outcomes are 1 year post-partum
[C] Estimated from available data

Combined Vitamin D and Calcium and Health Outcomes

Women's Health Initiative (WHI) trial.

The WHI trial provided data for numerous health outcomes of interest. For this reason and because of some methodological issues unique to this trial, the study is discussed here. The trial compared combined vitamin D_3 400 IU and calcium carbonate 1000 mg daily versus placebo in a 7 year trial in 36,282 postmenopausal women (age 50-79 y). The Tufts EPC, members of the Technical Expert Panel, and reviewers of the draft report debated about the quality of this trial. It was generally agreed that the overall methodological rigor and analyses were of good quality for most outcomes. However, there was not complete consensus on how to regard the fact that the women in both groups of this 7 year trial were allowed to take additional vitamin D supplements up to 600 IU and later 1000 IU per day and calcium supplements up to 1000 mg per day. At baseline, about one-third of women in both supplement and placebo groups were taking vitamin D supplements of at least 400 IU/d and 29 percent were taking at least 500 mg/d of supplemental calcium; by the end of the trial 69 percent of women were taking any additional supplemental calcium. During the 7 years, only about 60 percent of women (in any given year) were taking at least 80 percent of the study pills; at the end of the trial, only 76 percent were still taking any study medications. Regarding the overall quality of the study, arguments were put forward that this was a high quality effectiveness trial (in contrast with a more standardized efficacy trial) and thus had increased relevance to the actual use of supplements, that the crossover of interventions affects the applicability more than the methodological quality, and that the trial should not be downgraded because data reporting was more complete than for most trials. However, it was the consensus among the Tufts EPC that overall, the methodological quality of the trial was B, particularly when the trial is being used to guide decisions about DRI, as opposed to decisions about whether to actively recommend supplementation for an individual woman.

Combined Vitamin D Calcium and Growth

We reviewed primary studies that evaluated relationships between vitamin D and growth parameters in infants and children.

Synopsis.

One C-rated nonrandomized study 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.

Detailed presentation (Tables 4 & 6).

Infant 0 - 6 months; 7 months - 2 years; pregnant or lactating women.

We identified a study from India that included a nonrandomized comparison between combined vitamin D (1200 IU/d) and calcium (375 mg/d) for the expectant mothers versus no supplementation. The outcome was infant birth weight.[41] This study has already been described in the "Vitamin D and growth" section, as it also included a vitamin D only intervention arm. The study included expectant mothers with daily milk intake less than 500 mL and estimated daily vitamin D intake less than 30 IU. It was rated C for methodological quality, because of the lack of randomization and incomplete reporting of analyses. According to the reported analysis,

infants of women who received supplementation were significantly heavier at birth by 160 g on average (95 percent CI 0, 320).

Findings by life stage

- **0 – 6 mo** 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 by 160 g on average (95 percent CI 0, 320). (See also the Pregnant & lactating women.)
- **7 mo – 2 y** No identified study covered this life stage.
- **3 – 8 y** No identified study covered this life stage.
- **9 – 18 y** No identified study covered this life stage.
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed
- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** 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 by 160 g on average (95 percent CI 0, 320). (See also the 0 – 6 mo category.)

Combined Vitamin D and Calcium and Cardiovascular Disease

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and cardiovascular events. A variety of cardiovascular events after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined daily vitamin D_3 400 IU and calcium carbonate 1000 mg versus placebo in 50 to 79 year old women. No statistically significant effect was found with combined vitamin D and calcium supplementation on any cardiovascular outcome. However, near significant associations were found for three outcomes, suggesting increased risk with supplementation for a composite cardiac outcome that included invasive cardiac interventions, invasive cardiac interventions, and transient ischemic attacks. No significant associations were found for cardiovascular death, a composite cardiac outcome (myocardial infarction or cardiac death), coronary heart disease death, myocardial infarction, hospitalization for heart failure, angina, combined stroke or transient ischemic attack, stroke alone, or cerebrovascular death.

Detailed presentation (Tables 85 & 86).

In the WHI trial, discussed above, the evaluated cardiovascular outcomes were all prespecified secondary outcomes.[199,200] On average, the women had normal blood pressure. There were no significant effects of the supplementation on any of the outcomes, though three of the outcomes did approach statistical significance suggesting increased events with supplementation: composite cardiac events (HR = 1.08 [95 percent CI 0.99, 1.19]), coronary artery bypass grafting or percutaneous coronary interventions (HR=1.09 [95 percent CI 0.98, 1.22]), and transient ischemic attacks (HR=1.16 [95 percent CI 0.95, 1.42]). The authors, however, concluded that calcium and vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy postmenopausal women. The outcomes cardiac death and stroke were evaluated by age decade. No interaction was found with age (no significant difference across age groups). A similar analysis based on total calcium intake (dietary plus supplemental) also found no interaction.

Findings per intake level.

No conclusions are possible about a dose effect from this single study, especially since the women were allowed to take additional concurrent calcium and vitamin D supplements. However, no interaction was found with total reported calcium intake.

Findings by age and sex.

The study investigated postmenopausal women 50 to 79 years old. No interaction of effects with decade of age was found.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data available

- **51 – 70 y** One large trial that included women mostly within this life stage (WHI) found no significant effect of combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) on cardiovascular outcomes after 7 years.
- **≥71 y** Inadequate available data.
- **Postmenopause** All women in the WHI trial were postmenopausal. See 51-71 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 85. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Hsia 2007[199] LaCroix 2009[200] WHI US (various) [17309935 19221190]	• Health status • Mean age (range), y • Male (%)	Any 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group Low Ca intake (<800 mg/day): 34%	Combined Vit D & Ca supplement vs. Placebo	See page 242	

Table 86. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Hsia 2007[199] LaCroix 2009[200] WHI [17309935 19221190]	50-79 y, Women	Cardiovascular death	2°	7	Vit D + Ca	226	18,176	HR (Suppl/Placebo)	0.92*	0.77, 1.10	NS	B
					Placebo	244	18,106					
		Cardiac composite (MI, CHD death, CABG, or PCI)	2°		Vit D_3 400 IU + Ca carbonate 1000 mg	920	18,176	HR	1.08	0.99, 1.19	0.10	
					Placebo	841	18,106					
		Cardiac composite (MI or CHD death)	2°		Vit D + Ca	499	18,176	HR	1.04	0.92, 1.18	0.50	
					Placebo	475	18,106					
		CHD death	2°		Vit D + Ca	130	18,176	HR	1.01*	0.79, 1.29	0.92	
					Placebo	128	18,106					
		MI	2°		Vit D + Ca	411	18,176	HR	1.05	0.91, 1.20	0.52	
					Placebo	390	18,106					
		CABG or PCI	2°		Vit D + Ca	674	18,176	HR	1.09	0.98, 1.22	0.12	
					Placebo	607	18,106					
		Hospitalized for heart failure	2°		Vit D + Ca	394	18,176	HR	0.95	0.83, 1.10	0.50	
					Placebo	407	18,106					
		Angina	2°		Vit D + Ca	404	18,176	HR	1.08	0.94, 1.24	0.30	
					Placebo	377	18,106					
		Cerebrovascular composite (Stroke or TIA)	2°		Vit D + Ca	563	18,176	HR	1.02	0.91, 1.15	0.75	
					Placebo	547	18,106					
		Stroke	2°		Vit D + Ca	362	18,176	HR	0.95	0.82, 1.10	0.51	
					Placebo	377	18,106					
		TIA	2°		Vit D + Ca	213	18,176	HR	1.16	0.95, 1.42	0.13	
					Placebo	182	18,106					
		Cerebrovascular death	2°		Vit D + Ca	213	18,176	HR	0.89*	0.62, 1.29	NS	
					Placebo	182	18,106					

Combined Vitamin D and Calcium and Body Weight

We searched for systematic reviews and primary studies that evaluated associations between combined vitamin D and calcium and *incidence of overweight or obesity*; no such studies were found. For the outcome *weight change* (in kilograms or body mass index units), we included only randomized controlled trials. The EPC and the TEP agreed that the limited resources would not be expended on reviewing observational studies for the surrogate outcome body weight (where overweight or obesity are considered to be the clinical outcomes). We included only studies of adults. Studies of weight gain in children are included in the "Growth" section.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and body weight in adults. One RCT each tested the effect of combined vitamin D and calcium in the setting of either an isocaloric diet or an energy restricted diet. Both used vitamin D_2 400 IU/d and calcium carbonate (one 1000 mg/d, one 1200 mg/d) and were restricted to women. In the WHI trial of postmenopausal women on an isocaloric diet after 7 years, there was a statistically significant 0.1 kg smaller weight gain in those assigned to the supplement. The effect was statistically similar across age groups. In a Quebec study of 63 overweight premenopausal women, the apparent effect of supplementation in the setting of an energy restricted diet was greater than the WHI trial (net change -1.0 kg), but this was not a significant difference between the supplement and placebo groups.

Detailed presentation (Tables 87 & 88).

Isocaloric diet.

The WHI trial was analyzed for the effect of daily combined vitamin D_2 400 IU and calcium carbonate 1000 mg on weight.[201] The trial included about 36,000 postmenopausal women aged 50 to 79 years. The methodological quality of the study was B. At 7 year followup, the net change in body weight (supplemented minus control) was -0.13 kg (95 percent CI -0.21, -0.05; less weight gained in supplement group). This was of questionable clinical significance, but was statistically significant. The investigators performed numerous subgroup analyses including those based on age. There were no substantive or statistically significant differences among the evaluated age subgroups.

Energy restricted diet.

A trial performed in Quebec City analyzed 63 premenopausal overweight or obese women (mean age 43) comparing daily vitamin D_2 400 IU and calcium carbonate 1200 mg versus placebo.[202] Women in both study groups were placed on a weight-loss intervention which consisted of a 700 Kcal/day decrease in energy intake for 15 weeks; the women met biweekly with a nutritionist. The trial was rated methodological quality C due to a high drop out rate (25 percent) and poor description of the methodology. Women in both study groups on average lost weight, with those in the supplement group losing 1.0 kg more (4 vs. 3 kg). However, this effect was not statistically significant (P=0.19).

Findings per vitamin D and calcium dose.

No conclusion could be reached about a possible effect of vitamin D and calcium dose.

Findings per age and sex.

The trials included only women. The effect of supplementation on postmenopausal women not on an energy restricted diet was of questionable clinical significance after 7 years. The effect of supplementation for 15 weeks on overweight and obese premenopausal women (in an approximate age range of 32 to 54 years) on an energy restricted diet was relatively large (-4 vs. -3 kg), but this difference between the supplemented and control groups was not statistically significant.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** A single trial of women on an energy restricted diet found a nonsignificant difference in weight loss between that those assigned to vitamin D 300 IU and calcium 1200 mg supplementation for 15 weeks.
- **51 – 70 y** The WHI trial found no clinically significant effect on weight of vitamin D 300 IU and calcium 1000 mg after 7 years.
- **≥71 y** The subgroup of women in the WHI trial in this life stage had a similar net weight change as all the study participants as a whole, but the effect was not statistically significant.
- **Postmenopause** All the women in the WHI trial were postmenopausal.
- **Pregnant & lactating women** Not reviewed

Table 87. Combined vitamin D and calcium and weight: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Caan 2007[201] WHI US (various) [17502530]	• Health status • Mean age (range), y • Male (%)	All, post-menopause 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group	Vit D & Ca carbonate vs. Placebo	See page 242	Factorial design with HT vs. Placebo
Major 2007[202] Quebec City, Canada (47°N) [17209177]	• Health status • Mean age (range/SD), y • Male (%)	Overweight, healthy, pre-menopause 43 (5.5) 0	Ca 704 mg/d	Vit D + Ca carbonate vs. Placebo	nd	Energy restriction

Table 88. Combined vitamin D and calcium and weight: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex (Subgp)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Isocaloric Diet														
Caan 2007[201] WHI [17502530]	50-79 y, Women	Weight	2°	7 y	Vit D_2 400 IU + Ca carbonate 1000 mg	18,129	kg	76.0	nd	nd	-0.13	-0.21, -0.05	.001[A]	B
					Placebo	18,055		75.9	nd	nd				
	(50-54 y)				Vit D_3 + Ca	2592	kg	nd	nd		-0.24	-0.45, -0.03	<0.05[B]	
					Placebo	2561		nd	nd					
	(55-59 y)				Vit D_3 + Ca	4134	kg	nd	nd		-0.08	-0.24, +0.09	NS	
					Placebo	4135		nd	nd					
	(60-69 y)				Vit D_3 + Ca	8276	kg	nd	nd		-0.15	-0.27, -0.03	<0.05	
					Placebo	8243		nd	nd					
	(70-79 y)				Vit D_3 + Ca	3174	kg	nd	nd		-0.10	-0.27, +0.09	NS	
					Placebo	2561		nd	nd					
	(White)				Vit D_3 + Ca	15,047	kg	nd	nd		-0.13	-0.22, -0.04	<0.05[C]	
					Placebo	15,106		nd	nd					
	(Black)				Vit D_3 + Ca	1682	kg	nd	nd		-0.32	-0.59, -0.06	<0.05	
					Placebo	1635		nd	nd					
	(Hispanic)				Vit D_3 + Ca	789	kg	nd	nd		-0.08	-0.48, +0.32	NS	
					Placebo	718		nd	nd					
	(Asian / Pacific Islander)				Vit D_3 + Ca	369	kg	nd	nd		+0.19	-0.37, +0.75	NS	
					Placebo	353		nd	nd					
Energy Restricted Diet														
Major 2007[202] Quebec City, Canada [17209177]	43 (SD)	Weight	2°	15 wk	Vit D_2 400 IU + Ca carbonate 1200 mg	30	kg	81.5	-4.0	+-9.0	-1.0	-2.31. +0.31	0.19	C
					Placebo	33		83.6	-3.0	+-11.7				

[A] In addition, subgroup analyses by baseline BMI and baseline dietary calcium intake are reported.
[B] No statistically significant interaction with age.
[C] No statistically significant interaction with ethnicity.

Combined Vitamin D and Calcium and Cancer

Cancer from all causes and total cancer mortality.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and total cancer incidence or mortality. Two RCTs reported different effects of combined vitamin D_3 and calcium supplementation on the risk of total cancer. The WHI showed no effects,[71] while the trial conducted in Nebraska (latitude 41°N) reported significant reduction of risk of total cancer.[52] However, both vitamin D doses and baseline vitamin D status were substantially different between these two RCTs. Therefore, the effects from these two RCTs were not comparable.

Detailed presentation (Tables 89 & 90).

The 7-year WHI trial that enrolled 36,282 postmenopausal women across the US compared a daily supplement of vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo and evaluated incidence of total cancer and total cancer mortality as part of multiple secondary analyses.[71] The median serum 25(OH)D level of the study population was 42 nmol/L. The trial did not find significant effect of combined vitamin D_3 and calcium supplementation on either the risk of total cancer (adjusted HR: 0.98, 95 percent CI 0.91, 1.05) or total cancer mortality (adjusted HR: 0.89, 95 percent CI 0.77, 1.03). The methodological quality of this study was rated B.

A 4-year population based RCT,[52] sampled from a 9-county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d), or calcium alone (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d), compared to placebo in reducing the incidence of fracture. Incidence of cancer was a secondary outcome in this trial. A total of 734 postmenopausal women, aged more than 55 years old, were analyzed for the effect of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d). The mean 25(OH)D concentration at baseline was 72 nmol/L. Compared to the placebo group, the relative risk of developing cancer at the end of study was 0.40 (95 percent CI 0.20, 0.82; P=0.013) for the vitamin D_3 plus calcium group. On the hypothesis that cancers diagnosed early in the study would have been present, although unrecognized at entry, the analyses were restricted to women who were free of cancer at 1 year intervention. The relative risk of developing cancer at the end of study for the vitamin D_3 plus calcium group changed to 0.23 (95 percent CI 0.09, 0.60; P= 0.005). The methodological quality of this study was rated B.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** No data
- **51 – 70 y** No data
- **≥71 y** No data

- **Postmenopause** The WHI trial using vitamin D_3 400 IU/d plus calcium carbonate 1000 mg/d showed no effects, while the trial in Nebraska using vitamin D_3 1000 IU/d plus calcium citrate or carbonate 1500 mg/d showed significant reduction of risk of total cancer.
- **Pregnant & lactating women** No Data

Table 89. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006[71] WHI US (various) [16481636]	• Health status • Mean age (range/SD), y	Post-menopausal women nd (50-79)	Ca intake (mg/d): <800, 34%; 800-200, 26%; ≥1200, 40% Median 25(OH)D: 42 nmol/L	Vit D_3 400 IU/d + Ca 1000 mg/d vs. Placebo	See page 242	
Lappe 2007[52] Nebraska, US (41º N) [17556697]	• Health status • Mean age (range/SD), y	Mentally and physically fit; post-menopause 67 (7.3)	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo	nd	

Table 90. Combined vitamin D and calcium and total cancer incidence: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Followup, year	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Wactawski-Wende 2006[71] WHI [16481636]	Post-menopausal women	Incident cancer (all causes)	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	1634	18176	Adjusted HR (Vit D+Ca)/placebo	0.98	0.91, 1.05	0.53	B
					Placebo	1655	18106					
	Post-menopausal women	Total cancer mortality	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	344	18176	Adjusted HR (Vit D+Ca)/placebo	0.89	0.77, 1.03	0.12	
					Placebo	382	18106					
Lappe 2007[52] [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	13	446	RR (Vit D+Ca)/placebo	0.40	0.20, -0.82	0.01	B
					Placebo	20	288					
	Post-menopausal women	Incident cancer (restrict to subjects who were free of cancer at 1 y intervention)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	8	403	RR (Vit D+Ca)/placebo	0.23	0.09, -0.60	<0.005	
					Placebo	20	288					

Colorectal cancer.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and colorectal cancer mortality or incidence. One B quality RCT of postmenopausal women reported no significant association between supplemental vitamin D_3 and calcium and, colorectal cancer mortality or incidence.

Detailed presentation (Table 91 & 92).

The WHI compared daily supplemental vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo in 36,282 postmenopausal women. Colorectal cancer was evaluated as a secondary endpoint.[71] The primary endpoint was the prevention of hip fracture. At 7 years vitamin D_3 and calcium supplementation had no significant effect on colorectal cancer mortality (P=0.39) or incidence (P=0.51). In a subgroup analysis, risks of colon cancer and rectal cancer were also not significantly different between the supplemented and unsupplemented groups (P=0.99 and P=0.11, respectively). This trial was rated B because it did not restrict the participants from taking calcium or vitamin D supplements; they had mean daily total calcium intake of 1151 mg and vitamin D intake of 367 IU at enrollment.

Findings per special populations.

The WHI performed 18 subgroup analyses based on baseline participant characteristics including ethnic groups, body mass index, smoking status, and geographic regions according to solar irradiance.[71] No significant interactions were found with these baseline characteristics. The same RCT with multifactorial design reported an interaction between estrogen alone or combined estrogen and progestin therapy, and combined vitamin D and calcium supplementation for colorectal cancer risk in a post hoc analysis.[203] Among women concurrently assigned to hormone replacement therapies, colorectal cancer incidence was increased in the combined supplemental vitamin D and calcium arm compared to placebo (HR 1.50, 95 percent CI 0.96, 2.33), whereas among those concurrently assigned to placebo in the estrogen trials, colorectal cancer risk was reduced in the vitamin D plus calcium arm compared to placebo (HR 0.71, 95 percent CI 0.46, 1.09) (P for interaction = 0.02).

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data
- **51 – 70 y** One trial that included women mostly within this life stage (WHI) found no significant association between combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) and colorectal cancer mortality or incidence.
- **71+** The WHI included some people within this life stage, but no study adequately evaluated this life stage.

- **Postmenopause** The WHI exclusively focused on postmenopausal women. The study found no association between vitamin D and calcium intake and colorectal cancer mortality or incidence.
- **Pregnant & lactating women** Not reviewed

Table 91. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006[71] WHI US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Post-menopausal women nd (50-79) 0	Total Ca intake (mg/d) (Mean for both groups: 1151) Ca + Vit D arm: 1148 • <800: 34% • 800-<1200: 26% • ≥1200: 39% Placebo arm: 1154 • <800: 33% • 800-<1200: 26% • ≥1200: 40% Total Vit D intake (IU/d) (Mean for both groups: 367) Ca + Vit D arm: nd • <200: 38% • 200-<400: 19% • 400-<600: 23% • 600: 19% Placebo arm: nd • <200: 37% • 200-<400: 19% • 400-<600: 24% • 600: 19%	Ca 1000 mg/d + Vit D_3 400 IU/d vs. Placebo	See page 242	The outcomes were based on self-reported questionnaires. Only colorectal cancers were verified centrally. Colorectal cancer screening was not mandated in the protocol. Lost to followup: • Ca + Vit D arm: 0.8% • Placebo arm: 0.8% Withdrawn: • Ca + Vit D arm: 1.9% • Placebo arm: 1.8%

Table 92. Combined vitamin D with calcium and colorectal cancer: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Wactawski-Wende 2006[71] WHI [16481636]	Post-menopausal women	Colorectal cancer mortality	2°	7	Vit D3 400 IU + Ca carbonate 1000 mg	34	18,176	HR (Suppl/Placebo)	0.82	0.52, 1.29	0.39	B
					Placebo	41	18,106					
		Colorectal cancer	2°		Vit D + Ca	168	18,176	HR	1.08	0.86, 1.34	0.51	
					Placebo	154	18,106					
		Colon cancer	2°		Vit D + Ca	128	18,176	HR	1.00	0.78, 1.28	0.99	
					Placebo	126	18,106					
		Rectal cancer	2°		Vit D + Ca	44	18,176	HR	1.46	0.92, 2.32	0.11	
					Placebo	30	18,106					

Colorectal adenoma. Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and incidence of intestinal adenoma. One B quality RCT of postmenopausal women found no significant effect of combined vitamin D_3 and calcium supplements on the incidence of colorectal adenoma. Another B quality post hoc subgroup analysis of a secondary prevention trial of adenomatous adenoma reported that calcium supplemented patients with higher baseline 25(OH)D concentrations had significantly lower risk of relapse compared to placebo (interaction P = 0.01 between subgroups). In contrast, no significant difference in relapse rates was found in calcium supplemented patients with lower baseline 25(OH)D concentrations compared to placebo.

Detailed presentation (Table 91 & 92).

The WHI compared a daily supplement of vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo and evaluated incidence of self-reported colorectal adenoma as part of multiple secondary analyses.[71] At 7 years, the incidence of adenoma was not significantly different between the supplement and placebo groups (p=0.71). All the adenoma cases were based on self-reported data, not verified by medical record review or histopathology report.

A post hoc subgroup analysis of the CPP trial of secondary adenoma prevention on the basis of calcium supplementation (1200 mg of elemental calcium) evaluated the risk of colorectal adenoma stratified by baseline 25(OH)D concentrations.[204] The primary endpoint of the original trial was the risk of recurrent adenoma. After 4 years, in the subgroup with 25(OH)D concentrations greater than 72.6 nmol/L at baseline, subjects who received supplemental calcium had a significantly lower incidence of recurrent adenoma compared to placebo (HR=0.71 [95 percent CI 0.57,0.89] versus HR=1.05 [95 percent CI 0.85, 1.29]; interaction P=0.01). In the subgroup with 25(OH)D concentrations lower than 72.6 nmol/L, the risk of recurrence was not significantly different between supplemental calcium and placebo. No subgroup data were available regarding sex, separate life stages, or other special populations (e.g., obese, smokers, ethnic groups, or users of contraceptives).

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **51 – 70 y** The analysis of the CPP with a mean age of 61 years included participants mostly within this life stage. The study found a significant association between supplemental calcium and reduced risk of colorectal adenoma in a subgroup with 25(OH)D concentrations higher than 72.6 nmol/L.
- **71+** The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **Postmenopause** The WHI found no association between combined vitamin D_3 and calcium supplements and the incidence of colorectal adenoma.
- **Pregnant & lactating women** Not reviewed

Breast cancer

Synopsis

No qualified systematic reviews evaluated the association between vitamin D and calcium intake, body stores, or serum concentrations, and breast cancer. Breast cancer incidence and breast cancer related mortality after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined daily vitamin D_3 400 IU and calcium carbonate 1000 mg versus placebo in 50 to 79 year old women without a prior history of breast cancer.[205] No statistically significant effect was found with combined vitamin D and calcium supplementation on incident breast cancer outcome. No significant associations were found for breast cancer related mortality.

Detailed presentation (Tables 93 & 94)

In the WHI trial, the evaluated breast cancer incidence and breast cancer related mortality outcomes were secondary outcomes.[205] There were no significant effects of combined vitamin D and calcium supplementation on both outcomes. The authors concluded that invasive breast cancer incidence was similar in the two groups of healthy postmenopausal women: calcium and vitamin D supplementation and placebo groups. The relationship of 25(OH)D serum concentrations and the risk of breast cancer was examined in a nested case-control design. The study found no relationship between total vitamin D intake and 25(OH)D serum concentrations with the risk of breast cancer.

Findings per intake level

No conclusions are possible regarding a dose effect from this single study, especially since the women in the intervention and placebo groups were allowed to take additional concurrent calcium and vitamin D supplements.

Findings by age and sex

The study investigated postmenopausal women 50 to 79 years old.

Findings by life stage

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data available
- **51 – 70 y** The WHI trial that included women mostly within this life stage found no significant effect of combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) on incident breast cancer and mortality from breast cancer after 7 years.
- **≥71 y** Inadequate available data.
- **Postmenopause** All women in the WHI trial were postmenopausal.
- **Pregnant & lactating women** Not reviewed

Table 93. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Chebowski 2008[205] WHI US (various) [19001601]	• Health status • Mean age (range), y • Male (%)	No breast cancer 50-79 0	Baseline Ca supplementation: Vit D & Ca arm <800: 34.3% 800-<1200: 26.5% ≥1200: 39.3% Placebo arm <800: 33.8% 800-<1200: 26.2% ≥1200: 40.0% Baseline Vit D supplementation: Vit D & Ca arm Yes: 47.1% No: 52.9% Placebo arm Yes 47. 6% No 52.4%	Combined Vit D & Ca supplement vs. Placebo	See page 242	Intervention and placebo groups were allowed to take additional concurrent calcium and vitamin D supplements.

Table 94. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Chebowski 2008[205] WHI [19001601]	50-79 y, Women	Breast cancer incidence	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	668	18176	HR (Suppl/Placebo)	0.96	0.86, 1.07	NS	B
					Placebo	693	18106					
		Death from breast cancer	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	23	18176	HR	0.99	0.55, 1.76	NS	
					Placebo	23	18106					
		Invasive breast cancer – subgroup >67.6 baseline 25(OH)D	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	86	195	Adj OR	0.89	0.58, 1.36	NS	
					Placebo	76	185					
		Invasive breast cancer – subgroup 55.4-<67.6 baseline 25(OH)D	2°	7	Vit D_3 + Ca	95	171	Adj OR	1.25	0.83, 1.90	NS	
					Placebo	86	171					
		Invasive breast cancer – subgroup 43.9- <55.4 baseline 25(OH)D	2°	7	Vit D_3 + Ca	102	176	Adj OR	1.07	0.70, 1.62	NS	
					Placebo	92	195					
		Invasive breast cancer – subgroup 32.4-<43.9 baseline 25(OH)D	2°	7	Vit D_3 + Ca	71	185	Adj OR	0.69	0.45, 1.06	NS	
					Placebo	102	171					
		Invasive breast cancer – subgroup <32.4 baseline 25(OH)D	2°	7	Vit D_3 + Ca	94	171	Adj OR	0.91	0.60, 1.39	NS	
					Placebo	91	176					

Combined Vitamin D and Calcium and Pregnancy-related Outcomes

Preeclampsia.

Synopsis.

Based on data from a single RCT, there is no significant effect of combined vitamin D and calcium supplementation on the prevention of preeclampsia.

Detailed presentation (Tables 95 & 96.)

One RCT from India used a combination of vitamin D (1200 IU/d) and calcium (375 mg/d) for the prevention of preeclampsia.[206] **Table 85** describes the characteristics of the trial. The trial found no significant difference between the compared arms (**Table 86**). Note that this RCT was excluded from the meta-analysis of trials for preeclampsia in the calcium section.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** [see pregnant and lactating women]
- **51 – 70 y** Not applicable
- **71+** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Based on data from a single RCT, there is no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) supplementation on the prevention of preeclampsia.

Other pregnancy-related outcomes.

Synopsis.

We did not identify any eligible studies on the relationship of vitamin D with or without calcium and high blood pressure, preterm birth, or small for gestational age infant.

Table 95. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Marya 1987[206] India (29°N) [3623260]	• Health status • Age range, y	Any 20-35	Ca: 500 mg/d in in diet; Vit D: ~40 IU/d (unclear how it was quantified)	Combined Vit D (1200 IU/d) & Ca (375 mg/d) supplement vs. no supplement	nd	

Table 96. Combined vitamin D and calcium and preeclampsia: Results of RCTs

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Compari-son)	Result	95% CI	P Btw	Study Quality
Marya 1987[206] India (29°N) [3623260]	Pregnancy	Toxemia (preeclampsia)	1°	ND	Vit D (1200 IU) & calcium (375 mg)	12	200	RR (combined Vit D & Ca vs. nothing)	0.67	0.33, 1.35	0.26	C
					No supplement	18	200					

Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health

Rickets, fractures, falls, or performance measures.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34)**.[6] Because the Ottawa's EPC report did not have separate analyses for the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation are presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. Only RCTs qualified for inclusion.

Synopsis.

The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) plus calcium is effective in reducing fractures in institutionalized populations, but there is inconsistent evidence that supplemental vitamin D reduces falls in postmenopausal women and older men. Our update search did not identify new RCT examining the combined effect of vitamin D plus calcium supplementation on rickets, fractures, or falls in postmenopausal women and older men.

One study published after the Ottawa EPC report analyzed the performance measure outcomes in a small sample of postmenopausal women from WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo groups after 5 years of followup.[207] One RCT of premenopausal women, aged 17 to 35 years old, showed that 800 IU/d of vitamin D in combination with 2000 mg/d of calcium supplementation can reduce the risk of stress fracture from military training compared to placebo.[208]

Detailed presentation (Table 34, 97, 98 & 99).

One RCT of female Navy recruits, aged 17 to 35 years, aimed to determine whether supplementation with vitamin D (800 IU/d) plus calcium (2000 mg/d) can reduce the risk of stress fractures from military training near the Great Lakes (41°N).[208] The median dairy intake was <1 serving/day, which provided less than 300 mg of calcium. The combined supplementation significantly reduced the risk of stress fractures by 20 percent compared to placebo. The methodological quality of this study was rated B.

One study analyzed the performance measure outcomes in a sample of 2928 postmenopausal women from the WHI trial who had objective physical function measures.[207] The results showed that physical function, measured by grip strength, chair stands, and walking time, had generally declined in postmenopausal women who were assigned to either vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo group. However, women who had received vitamin D plus calcium supplementation showed less declines in walking time than those who had received placebo. The methodological quality of this study was rated C because only a small proportion of women from the WHI trial were in the analyses and their baseline characteristics were unclear.

From the Ottawa EPC Report: Fractures - Postmenopausal women and older men.

Fifteen RCTs examined the effect of either vitamin D_2 or D_3 alone or in combination with calcium on total, nonvertebral and hip fractures in postmenopausal women or older men. Few trials evaluated vertebral fractures. Most trials used vitamin D_3. There were no trials identified in premenopausal women.

Meta-analysis results from 13 RCTs of vitamin D_2 or D_3 with or without calcium showed a nonsignificant reduction in the risk of total fractures that persisted when only trials of higher quality were combined. Most trials used vitamin D_3. When combining seven RCTs of vitamin D_3 (400-800 IU) plus calcium, there was a reduction in the risk of total and hip fractures. However, in a subgroup analysis (800 IU vitamin D_3), this benefit was only evident in trials of institutionalized elderly subjects. One possible explanation for the discrepancy is that the mean serum 25(OH)D concentration achieved in trials of institutionalized participants was higher than in the trials on community dwellers. The combined estimate from trials with higher end-of-study serum 25(OH)D concentrations (>74 nmol/L) was consistent with a significant reduction in the risk of fractures.

In Ottawa EPC report: Falls - Postmenopausal women and older men.

Meta-analysis results from 12 RCTs demonstrated a small reduction in the risk of falls with supplemental vitamin D_2 or D_3 (oral or injectable) with or without calcium (OR 0.89, 95 percent CI 0.80, 0.99). The individual treatment effects ranged from OR 0.28 (95 percent CI 0.12, 0.67) to 1.16 (95 percent CI 0.70, 1.92). In the two cluster RCTs, one demonstrated a significant reduction in the risk of falls in postmenopausal women taking vitamin D_3 plus calcium (RR 0.88, 95 percent CI 0.79, 0.98), whereas the other trial did not show a significant reduction in the risk of falls in elderly individuals taking vitamin D_2 (RR 1.09, 95 percent CI 0.95, 1.25). Meta-analysis of eight RCTs of oral vitamin D_2/D_3 supplementation with calcium showed a reduction in the risk of falls, whereas four RCTs of oral vitamin D_3 alone did not. Subgroup analyses showed a significant reduction in the risk of falls when only trials of postmenopausal women were combined. Sensitivity analyses showed a significant reduction in the risk of falls when combining (1) RCTs that explicitly defined falls and the method of fall ascertainment and (2) those in which the allocation concealment was unclear. However, combining trials by degree of compliance and loss to followup did not.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) plus calcium is effective in reducing the risk of fractures in institutionalized populations, but there is inconsistent evidence that supplemental vitamin D reduces the risk of falls in postmenopausal women and older men. One RCT of female Navy recruit, aged 17 to 35 years old, showed that vitamin D (800 IU/d) in combination of calcium (2000 mg/d) supplementation can reduce the risk of stress fractures from military training compared to placebo.
- **51 – 70 y** No new data since the Ottawa report
- **71+** No new data since the Ottawa report

- **Postmenopause** One study analyzed the performance measure outcomes in a small sample of postmenopausal women from the WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation and placebo groups after 5 years of followup.
- **Pregnant & lactating women** No data

Table 97. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2008[208] Great Lakes, IL, US (41°N) [18433305]	• Health status • Mean age (range), y • Male (%)	Assumed healthy (Navy recruits) 19 (17-35) 0	Mean dairy servings/wk = 6 (ranged 1-26)	Vit D 800 IU/d + Ca 2000 mg/d vs. Placebo	Monitor pill taking: project staff observed the galley food lines, visited recruits in their quarters, and conducted an exit interview.	
Brunner 2008[207] WHI US (various) [18755319]	• Health status • Mean age (range), y • Male (%)	nd (for the sub sample from WHI trial) 50-79 0	nd	Vit D 400 IU/d + Ca 1000 mg/d vs. Placebo	nd (however, adherence was assessed at least annually from the weight of remaining pills along with a structured interview in WHI trial)	A sub sample from WHI trial. Post hoc analyses of a RCT.

Table 98. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lappe 2008[208] [18433305]	17-35 y women	Stress fracture from Navy training (ITT)	1°	2	Vit D 800 IU + Ca 200 mg	139	2626	RR (Vit D+Ca)/placebo	0.8	0.64, 0.99	0.026	B
					Placebo	170	2575					
		Stress fracture from Navy training (per protocol)	1°	2	Vit D 800 IU + Ca 200 mg	126	1852	Adjusted OR (Vit D+Ca)/placebo	0.79	0.62, 1.01	0.059	
					Placebo	160	1848					

Table 99. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures)

Author Year Study Name PMID	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Brunner 2008[207] [18755319]	Post-menopause	Grip strength	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1185	kg	22.81	-2.49	5.81	0.15	0.24	0.52	C
					Placebo	1162		22.96	-2.64	5.69				
		Chair stands	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1065	counts	6.52	-0.38	1.81	0.04	0.08	0.603	
					Placebo	1053		6.63	-0.43	1.81				
		Walking time	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1160	seconds		+0.26	6.28	-0.54	0.26	0.030	
					Placebo	1141			+0.81	6.43				

Combined Vitamin D and Calcium and all-cause Mortality

Synopsis.

This synopsis is based on a meta-analysis of RCTs of combined vitamin D and calcium supplementation evaluating mortality. Numerical data were extracted from previous systematic reviews. Most trials used daily regimens; in these trials, vitamin D doses ranged between 300 and 880 IU per day. Most trials combined vitamin D and calcium supplementation; when used, calcium doses ranged between 500 and 1200 mg per day.

Our meta-analysis of 11 RCTs (44,688 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.93, 95 percent CI 0.86, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses. Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity.

Although the meta-analyses suggest decreased risk for all-cause mortality with combined vitamin D and calcium supplementation, the relationship is not statistically significant in the performed analyses.

Detailed presentation (Table 37; Figure 22).

As mentioned in the Methods section, we updated and reanalyzed published meta-analyses of mortality outcomes. We drew our own conclusions based on our analyses. We also comment on the concordance of our conclusions with those of the published meta-analyses.

Relevant published systematic reviews of RCTs (with meta-analyses).

As described in the vitamin D and all-cause mortality section, we identified two potentially eligible systematic reviews,[83,84] and selected one as the basis for our reanalysis (Autier 2007).[83] Table 37 in the "Vitamin D" section summarizes the findings of the Autier 2007 systematic review.

As detailed below, we identified one additional trial of combined vitamin D and calcium supplementation reporting all-cause mortality.[209]

Eligible studies published after the systematic reviews.

The literature searches in Autier 2007 extended up to November 2006. We identified two additional RCT reports published after November 2006.[71,209] One publication[71] reported on the same trial as another publication[210] in the Autier 2007 meta-analysis, and was therefore excluded from our reanalysis. The other RCT (Bjorkman 2008[209]) was included in our meta-analysis.

One three-arm RCT (Bjorkman 2008[209], n=218) compared no supplementation versus daily supplementation with 400 IU and 1200 IU of vitamin D_3 and 500 mg of calcium. Mortality was assessed at 6 months. It included people older than 65 years, with chronically impaired mobility and stable general condition. The Bjorkman 2008 RCT was assigned grade "A" for overall reporting quality.

Reanalysis.

We excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,[85] one was published only in abstract form,[86] and in the last trial the controls also received supplementation with vitamin D, albeit with a smaller dose,[87] and two used injections of vitamin D.[88,89] Altogether, 11 RCTs were included in the reanalysis of combined vitamin D and calcium supplementation and all-cause mortality (i.e., 10 out of 18 in the Autier 2007 meta-analysis, and a subsequently published one[209]).

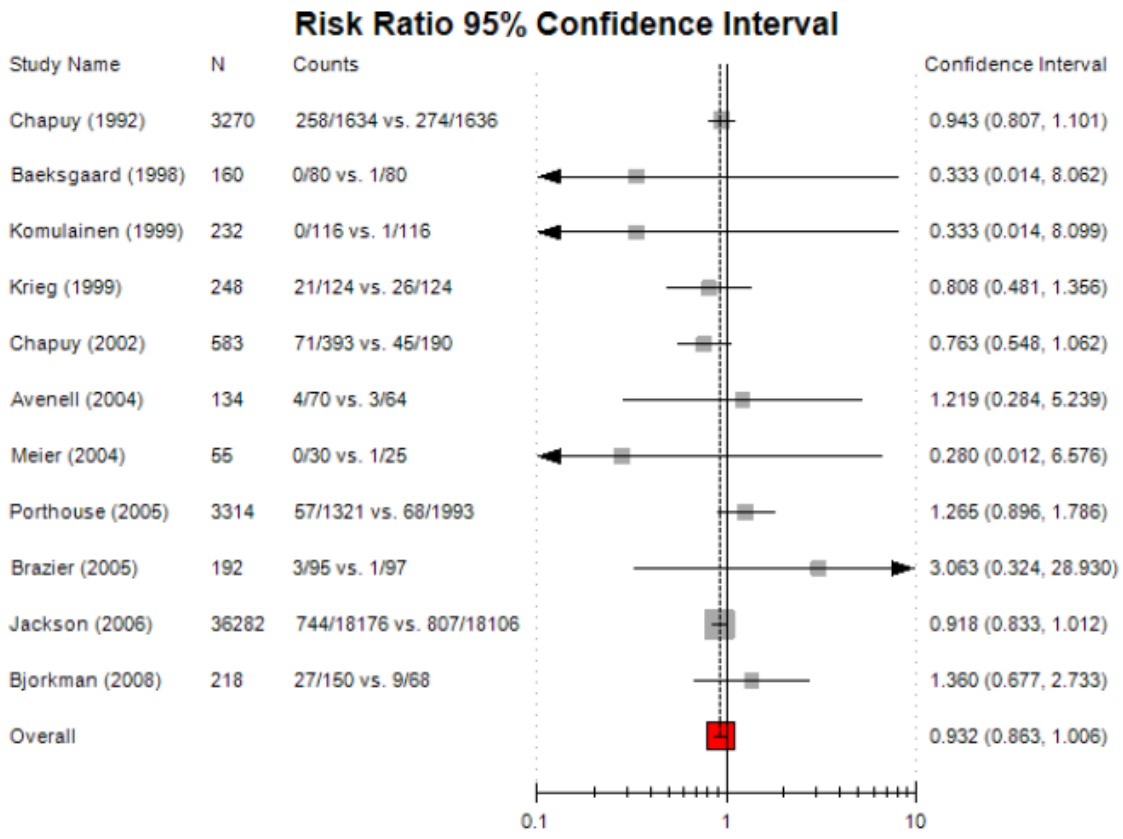
Among the 12 trials, sample sizes ranged from 55 to 36,282 participants, with 7 studies including more than 500 participants. Followup periods ranged from 6 to 84 months (median 24 months). Vitamin D doses in most trials ranged between 300 and 880 IU per day. One trial used 100,000 IU orally every 4 months. Calcium supplementation doses ranged between 500 to 1200 mg per day.

Overall, a meta-analysis of the 11 RCTs (44,688 participants; Figure 22) found no statistically significant relationship between vitamin D and all-cause mortality (RR=0.93, 95 percent CI 0.86, 1.01). There is little evidence for between-study heterogeneity in these analyses (P=0.58, I^2=0 percent). Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity (P=0.46, I^2=0 percent). There are no RCTs with mean participant age below 50 years. It is unclear whether these findings are directly applicable to other life stages. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95 percent CI 0.84, 1.15), with little evidence for between study heterogeneity (P=0.33, I^2=13 percent).

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** No data
- **51 – 70 y** Our meta-analysis of 12 RCTs (44,838 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.94, 95 percent CI 0.87, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses.
- **71+** The above are likely applicable here. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95 percent CI 0.84, 1.15), with little evidence for between study heterogeneity.
- **Postmenopause** Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity.
- **Pregnant & lactating women** No data

Figure 22. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality.



Combined Vitamin D and Calcium and Hypertension and Blood Pressure.

We reviewed systematic reviews and primary studies that evaluated associations between combined vitamin D and calcium intake and incidence of hypertension or change in blood pressure. For the outcome incidence of hypertension, we included RCTs and other longitudinal studies. For the outcome change in blood pressure, we included only RCTs. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the "Pregnancy-related outcomes" section.

Combined vitamin D and calcium and hypertension.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium intake, body stores, or serum concentrations and incidence of hypertension. The WHI trial reported an analysis of the risk of developing hypertension among the subset of women without hypertension at baseline. Over 7 years, combined vitamin D and calcium supplementation had no effect on the risk of hypertension.

Detailed presentation (Tables 100 & 101).

The WHI trial of a combined vitamin D_3 400 IU and calcium carbonate 1000 mg supplement daily versus placebo had methodological quality B for the blood pressure outcome. The 36,282 women were postmenopausal (age 50-79 y) with a background calcium intake on average of about 1150 mg/day (from diet and supplements).[211] The women were allowed to take additional concurrent calcium and vitamin D supplements. The analysis of incident hypertension was reported briefly in a larger analysis of the blood pressure outcome (see *Combined vitamin D and calcium and blood pressure*, below). Among 17,122 initially nonhypertensive women, 39 percent either were prescribed medication for hypertension or developed blood pressure above 140/90 mm Hg. The adjusted HR of developing hypertension over 7 years was 1.01 (95 percent CI 0.96, 1.06). Among 377 women with available data, there was a statistically significant trend across subgroups based on serum 25(OH)D concentration such that combined vitamin D and calcium supplementation *increased* the risk of developing hypertension more in those women with progressively *lower* baseline 25(OH)D ($P<0.01$ for trend). Other subgroup analyses based on age, race or ethnicity, weight, or baseline total calcium intake did not find any interactions with the effect of the supplement intervention.

Findings per intake level.

This single trial did not analyze different actual intake levels.

Findings by age and sex.

This trial found no difference in (lack of) effect by age among postmenopausal women.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data.

- **51 – 70 y** One large trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **≥71 y** The WHI trial included some women within the life stage, but no study adequately evaluated this life stage.
- **Postmenopause** All women in the WHI trial were postmenopausal. See 51-71 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 100. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008[211] WHI US (various) [18824662]	• Health status • Mean age (range), y • Male (%)	No HTN 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group 52% used Ca supplements 40% had intake ≥1200 mg/d (based on all subjects, including those with hypertension)	Combined Vit D + Ca supplement vs. Placebo	See page 242	Mean dose of open label supplemental Ca increased by <100 mg/d from 325 mg/d at enrollment; similar in both groups (based on all subjects, including those with hypertension)

Table 101. Combined vitamin D and calcium and incident hypertension: Results of RCTs

Author Year Study Name [PMID]	Life Stage [Subgp]	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Margolis 2008[211] WHI [18824662]	50-79 y, Women	HTN	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	3377	~8578	HR (Suppl/Placebo)	1.01	0.96, 1.06	0.69	B
					Placebo	3315	~8544					
	[25(OH)D <34.4 nmol/L]				Vit D + Ca	53			1.52	0.89, 2.59	NS	
					Placebo	38						
	[25(OH)D 34.4-47.6 nmol/L]				Vit D + Ca	39			1.48	0.89, 2.46	NS	
					Placebo	48						
	[25(OH)D 47.7-64.6 nmol/L]				Vit D + Ca	45			1.15	0.69, 1.92	NS	
					Placebo	45						
	[25(OH)D ≥64.7 nmol/L]				Vit D + Ca	48			0.79	0.51, 1.22	NS	
					Placebo	61						

Combined vitamin D and calcium and blood pressure.

Synopsis.

No qualified systematic reviews evaluated the association between vitamin D and calcium intake, body stores, or serum concentrations, and changes in blood pressure. Two RCTs compared combined vitamin D and calcium supplementation with placebo. Both the small trial of a combined vitamin D_3 400 IU and calcium carbonate 1200 mg supplement daily and the WHI trial found no significant effect of supplementation on blood pressure after 15 weeks or 6.1 years, respectively. The WHI trial analyzed blood pressure changes in a variety of subgroups, including by age, ethnicity, baseline total calcium intake, and baseline diagnosis of hypertension, but found no significant differences in effect across any subgroup.

Detailed presentation (Tables 102 & 103).

The WHI trial of a combined vitamin D_3 400 IU and calcium carbonate 1000 mg supplement daily versus placebo had methodological quality B for the blood pressure outcome. The 36,282 women were postmenopausal (age 50-79 y) with a background calcium intake on average of about 1150 mg/day (from diet and supplements).[211] On average, the women had normal blood pressure and were allowed to take additional concurrent calcium and vitamin D supplements. At 74 months, the women's mean systolic blood pressure had risen and diastolic blood pressure had fallen in both trial arms (by less than about 2 mm Hg each at 2 years[199]). The absolute changes were not significantly different in the women assigned to the supplement than placebo (net difference 0.2 mm Hg systolic and 0.1 mm Hg diastolic). In subgroup analyses there was no differences in results by age, ethnicity, baseline total calcium intake, baseline diagnosis of hypertension, or a variety of other factors.

The C quality trial of combined vitamin D and calcium, performed in Quebec City, recruited premenopausal women (mean age 43 y) with low calcium intake (800 mg calcium per day) who did not have severe hypertension (blood pressure over 160/95 mm Hg).[202] The mean baseline calcium intake was 704 mg/day. On average, the 63 women had normal blood pressure. They were given either combined vitamin D_3 400 IU and calcium carbonate 1200 mg daily or placebo. All women were on an energy restriction diet with a 700 kcal/day deficit. At 15 weeks, systolic and diastolic blood pressures were reduced in both study groups; systolic blood pressure was reduced by 2.5 mm Hg more in women on vitamin D and calcium than placebo, but this difference was not statistically significant. Diastolic blood pressure was reduced by the same amount in both groups. No subgroup analyses were reported. The study was limited by a 25 percent dropout rate due to lack of compliance with the diet and exercise portion of the trial, without performing an intention to treat analysis, an adequate description of the study methods, or a complete statistical analysis.

Findings per intake level.

Both trials used similar doses, vitamin D_3 400 IU and calcium carbonate 1000 or 1200 mg daily. The background calcium intake was lower in the study of premenopausal women (800 mg/day) than the WHI trial (1150 mg/day). The WHI trial found no significant difference in (lack of) effect in subgroups with different baseline total calcium intake.

Findings by age and sex.

Both the one small, short term, C quality trial of premenopausal women and the 6 year WHI trial of postmenopausal women found no effect. The WHI trial also found no difference in effect in subgroups of women based on age. No trials of men were found.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** One small trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **51 – 70 y** One large trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **≥71 y** The WHI trial included some women within the life stage, but no study adequately evaluated this life stage.
- **Postmenopause** All women in the WHI trial were postmenopausal. See 51-71 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 102. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008[211] WHI US (various) [18824662]	• Health status • Mean age (range), y • Male (%)	Any 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group 52% used Ca supplements 40% had intake ≥1200 mg/d	Combined Vit D + Ca supplement vs. Placebo	See page 242	Mean dose of open label supplemental Ca increased by <100 mg/d from 325 mg/d at enrollment; similar in both groups
Major 2007[202] Quebec City, Canada (47°N) [17209177]	• Health status • Mean age (SD), y • Male (%)	Healthy, Overweight, low Ca intake 43 (5.5) 0	Ca: ~704 mg/d; all <800 mg/d	Combined Vit D + Ca supplement vs. Placebo	nd	

Table 103. Combined vitamin D and calcium and blood pressure: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Margolis 2008[211] WHI [18824662]	50-79, Women	SBP	2°	6.1 y	Vit D_3 400 IU + Ca carbonate 1000 mg	18,176	mm Hg	127[A]	+1.1%[A]	0.9, 1.3	+0.22	-0.05, +0.49	0.11	B
					Placebo	18,106		128[A]	+0.7%[A]	0.5, 0.9				
Major 2007[202] Quebec City [17209177]	43 (5.5), Women	SBP	2°	15 wk	Vit D_3 400 IU + Ca carbonate 1200 mg (energy restriction diet)	30	mm Hg	112.4	-4.1	-6.5, -1.7	-2.5	-6.2, 1.2*	0.18	C
					Placebo (energy restriction diet)	33		109.5	-1.6	-4.2, 1.0				
DIASTOLIC BLOOD PRESSURE														
Margolis 2008[211] WHI [18824662]	50-79, Women	DBP	2°	6.1 y	Vit D_3 400 IU + Ca carbonate 1000 mg	18,176	mm Hg	76[A]	-0.2%[A]	-0.4, -0.02	+0.11	-0.04, +0.27	0.14	B
					Placebo	18,106		76[A]	-0.6%[A]	-0.8, -0.4				
Major 2007[202] Quebec City [17209177]	43 (5.5), Women	DBP	2°	15 wk	Vit D_3 400 IU + Ca carbonate 1200 mg (energy restriction diet)	30	mm Hg	74.9	-3.0	-4.8, -1.2	0	-2.7, 2.7*	1.0	C
					Placebo (energy restriction diet)	33		75.2	-3.0	-5.0, -1.0				

[A] Hsia 2007[199] [17309935]

Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34**).[6] Because the Ottawa's EPC report did not have separate analyses on the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation were presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. For adults, we included only BMD indices. For children, we included only BMC indices. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

One RCT found that, compared to placebo, there was no significant effect of supplementation with vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) on BMC changes in healthy girls, between 10 and 12 years.

Overall, findings from the Ottawa EPC report showed that vitamin D_3 ($\leq$ 800 IU/d) plus calcium (~500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck and total hip in predominantly populations of late menopausal women.[6] Two of the three new RCTs showed consistent findings in postmenopausal women, comparing vitamin D_3 or D_2 (300 or 1000 IU/d, respectively) plus calcium (1200 mg/d) to placebo.

Detailed presentation (Table 34, 104 & 105).

One RCT compared the effect of vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) supplementation to placebo on bone indices in healthy girls, aged 10 and 12 years.[212] The mean background dietary calcium intake was 670 mg/d. The intention-to-treat analyses showed that after 2 years of supplementation, there was no significant difference in the BMC changes between girls who received vitamin D plus calcium supplement or placebo. The methodological quality of this study was rated C, due to underpower and low compliance rate.

Three RCTs (two were rated B and one was rated C) examined the effect of vitamin D plus calcium supplementation on BMD changes. All three trials were conducted in postmenopausal women. However, the doses of vitamin D and calcium combinations varied. One RCT used daily dose of 400 IU vitamin D_3 plus 100 mg elemental calcium for 2 years [213] The second RCT used daily dose of 1000 IU vitamin D_2 plus 1200 mg calcium citrate for 5 years.[214] The third RCT used a daily dose of vitamin D_3 300 IU plus calcium citrate 1200 mg from calcium supplemented low-fat dairy products for 1 year.[215] The latter two RCTs resulted in a significant increase in hip or total BMD comparing vitamin D plus calcium supplementation to placebo.[214,215] The one RCT that did not show significant change in femoral neck BMD comparing vitamin D plus calcium supplementation to placebo used a substantially lower dose of calcium (100 mg/d) than the other two RCTs.

In Ottawa EPC report - Bone Mineral Density and women of reproductive age, postmenopausal women, and older men.

Overall, there is good evidence that vitamin D_3 plus calcium supplementation resulted in small increases in BMD of the spine, total body, femoral neck and total hip. Based on included

trials, it was less certain whether vitamin D_3 supplementation alone has a significant effect on BMD.

Seventeen RCTs evaluated the effect of supplemental vitamin D_2 or D_3 on BMD, predominantly in populations of late menopausal women. Only one small RCT included premenopausal women, and two trials included older men (> 60 years). Most trials were two to three years in duration and used vitamin D doses of ≤ 800 IU daily. Most trials used vitamin D_3 and also included calcium 500 mg as a cointervention.

Meta-analysis results of 17 RCTs of vitamin D_3 plus calcium versus placebo were consistent with a small effect on lumbar spine, femoral neck, and total body BMD. The WHI trial found a significant benefit of 400 IU vitamin D_3 plus 1000 mg calcium supplementation on total hip BMD. However, when the effect of vitamin D_3 plus calcium versus calcium alone supplementation is assessed, no significant increase in BMD was observed with either intervention, suggesting vitamin D_3 may be of less benefit in calcium replete postmenopausal women. Vitamin D_3 alone versus placebo did not result in a significant increase in BMD in postmenopausal women, except in one trial that noted an increase in femoral neck BMD. Only a few trials reported the impact of baseline serum 25(OH)D concentrations on BMD and in all of these trials, baseline 25(OH)D concentration was not associated with increased BMD.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** One RCT showed that, compared to placebo, there was no significant effect of vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) on BMC changes in healthy girls, aged between 10 and 12 years old.
- **19 – 50 y** No data
- **51 – 70 y** No new data since the Ottawa EPC report
- **≥71 y** No new data since the Ottawa EPC report
- **Postmenopause** Findings from the Ottawa EPC report showed that vitamin D_3 (≤ 800 IU/d) plus calcium (~500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip in predominantly populations of late menopausal women. Two of the three new RCTs showed a significant increase in hip or total BMD in postmenopausal women, comparing D_3 or D_2 (300 or 1000 IU/d, respectively) plus calcium (1200 mg/d) to placebo.
- **Pregnant & lactating women** No new data since the Ottawa EPC report

Table 104. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Cheng 2005[212] Jyvaskyla, Finland (62°24'N) [16280447]	• Health status • Mean age (range), y • Male (%)	Healthy 11.2 (10-12) 0	Diet Vit D: 100 IU/d Ca: 670 mg/d	Vit D_3 200 IU/d + Ca carbonate 1000 mg/d vs. placebo	65% completed intervention with >50% compliance	
Bolton-Smith 2007[213] (UK 54ºN) [17243866]	• Health status • Mean age (range), y • Male (%)	Healthy (assumed postmenopausal) 68 (≥60) 0	25(OH)D: 59.4 nmol/L Ca: 1548 mg/d	Vit D_3 400 IU/d + Elemental Ca 100 mg/d vs. placebo	Good supplement adherence based on pill count (median, 99; IQE 97.3-99.8%).	Noncompliant women were excluded.
Zhu 2008[214] CIFOS Western Australia [18089701]	• Health status • Mean age (SD), y • Male (%)	nd (assumed postmenopausal) 74.8 (2.6) 0	25(OH)D: 68.0 nmol/L Ca: 1010 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. placebo	No differences in adherence among groups (81-89% by tablet counting)	
Moschonis 2006[215] Greece (31ºN) [17181890]	• Health status • Mean age (range), y • Male (%)	Postmenopausal 61 (55-65) 0	Diet Vit D: 23.6 IU/d Ca 680 mg/d	Vit D_3 300 IU/d + Ca 1200 mg/d (from low fat dairy products) vs. control (usual diet)	Dairy group 93% (assessed via information obtained at the biweekly sessions	Control group had no intervention (or usual diet) so compliance issue not applicable

Table 105. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report

Author Year Study Name PMID	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Cheng 2005[212] [16280447]	10-12 y girls	BMC	1°	24	Vit D 200 IU + Ca carbonate 1000 mg	46	kg	1.3	34.7%	34.3%, 35.1%	-0.3%	-0.8, 0.2[A]	NS	C
					Placebo	39		1.3	35.0%	34.6%, 35.4%				
Bolton-Smith 2007[213] [17243866]	Postmenopausal women	Femoral neck BMD	nd	24	Vit D_3 400 IU + Elemental Ca 100 mg	50	mg/cm^2	nd	+1.9	-6.5, 10.3	+1.2	-12.6, 15.0[A]	NS	B
					Placebo	56		nd	+0.7	-10.2, 11.6				
Zhu 2008[214] Australia CIFOS [18089701]	Postmenopausal women	Hip BMD	1°	60	Vit D_2 1000 IU + Ca citrate 1200 mg	39/33[B]	mg/cm^2	783	nd		+2.2%	1.9, 2.5	0.05	B
					Placebo	41/36[B]		828	nd					
Moschonis 2006[215] [17181890]	Postmenopausal women	Total body BMD	1°	12	Vit D_3 300 IU + Ca 1200 mg (from low fat dairy products)	39	mg/cm^2	1.13	1.5%	0.9%, 2.2%	+2.2%	1.3, 3.1[A]	<0.05	C
					Control (usual diet)	36		1.12	-0.7%	-1.4%, -0.1%				

[A] Estimated from reported data.
[B] Baseline/follow-up number of subjects analyzed

How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D concentrations (arrow 4)?

The evidence for this question comes from studies identified in our literature search that crossed vitamin D terms with various outcomes terms. Studies that addressed this question but do not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all vitamin D supplements full text articles (in excess of 10,000) to look for serum 25(OH)D concentration data. Given that there is no plausible reason for a systematic bias of studies of a specific outcome choosing to report serum 25(OH)D concentration, we believe that the evidence found, while not comprehensive, is a small but representative random sample. Only RCTs were included for this question. RCTs of different regimens but with the same dose of vitamin D supplementation were excluded (e.g., comparison of daily, weekly versus monthly dose).

This question was also addressed in the Ottawa EPC report.[6] When appropriate, we extracted relevant data from the Ottawa EPC report to be incorporated into our analyses.

RCTs on Dietary Intakes of Vitamin D From Fortified Foods and Serum 25(OH)D Concentrations.

Synopsis.

Our updated search did not identify new RCT evaluating the effect of food fortification on serum 25(OH)D concentrations since the Ottawa EPC report.[6] The Ottawa EPC report concluded that there is "good" evidence that dietary intake of vitamin D increases serum 25(OH)D concentrations among adults.

Detailed presentation.

Ottawa EPC report –Adults.

There were eleven RCTs (n=1281) of which seven (n=668) permitted a quantitative analysis. Ten of eleven trials found a significant effect of dietary intake from foods fortified with vitamin D on serum 25(OH)D concentrations. There was significant heterogeneity of the treatment effect. Potential sources of heterogeneity are the different 25(OH)D assays used (two studies each used HPLC, RIA or CPBA, and one study did not report the assay), the dietary vehicles used, and study populations. The increase in serum vitamin D concentration in the seven trials ranged from 15 (95 percent CI 11, 18) to 40 (95 percent CI 25, 55) nmol/L (fortification consisting of 100 - 1000 IU of vitamin D).

There can be a potential confounding of the data by the food source, the assay used to measure 25(OH)D and potential differences in the bioavailability and/or metabolism of vitamin D_2 versus vitamin D_3. Most studies in this review used dairy products as the

source of fortified food. It is important to note that there is potential for study contamination through altered intake of other nutrients such as calcium, phosphate and acid load that can affect the study outcomes.

RCTs on Vitamin D Supplementation and Serum 25(OH)D Concentrations.

Synopsis.

Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. We believe that studies summarized here is a small but representative random sample of all available data.

We plot 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 D_3 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 in the plot. It is important to note that the studies had varied compliance rates in the vitamin D intake; limited or no adjustment for skin pigmentations, calcium intake, or background sun exposure; different vitamin D assay methodologies and measurement (both intra- and interassay) variability. All these factors increase the heterogeneity and limit the usefulness of an overall summary estimate for an intake dose response in serum 25(OH)D concentration. Nonetheless, the relationship between increasing doses of vitamin D_3 with increasing net change in 25(OH)D concentration was evident in both adults and children (Figure 23). It was also apparent that the dose-response relationships differ depending on study participants' serum 25(OH)D status ($\leq$40 vs. >40 nmol/L) at baseline (Figure 24), and depending on duration of supplementation ($\leq$3 vs. >3 months) (Figure 25).

Vitamin D_2 supplementation was more commonly used in RCTs of infants and pregnant or lactating women, than vitamin D_3 supplementation. Results showed that supplementation of vitamin D_2 significantly increased 25(OH)D concentrations in infants, lactating mothers and in cord blood.

Detailed presentation (Table 106; Figures 23, 24 & 25).

The results from 26 RCTs with 28 comparisons in adults and two RCTs with three comparisons in children evaluating the effect of vitamin D_3 supplementation alone or in combination with calcium supplementation on serum 25(OH)D concentrations were shown in Table 106. Most of the data were extracted directly from the Ottawa EPC report. In adults, the doses of vitamin D_3 ranged from 200 to 5000 IU/d, and the doses of calcium supplementation ranged from 500 to 1550 mg/d across the 25 comparisons. In children, the doses of vitamin D_3 ranged from 200 to 2000 IU/d across the three comparisons. Duration of supplementation ranged from 0.5 to 60 months. Study populations and baseline vitamin D concentrations varied across these comparisons.

Ottawa EPC report – Infants.

Seven RCTs included infants and few trials used vitamin D_3 supplementation. One RCT concluded that 200 IU of vitamin D_2 may not be enough to prevent vitamin D deficiency in those infants residing at northern latitudes. A dose-response relationship

was noted in this trial (100, 200, 400 IU/day). Consistent responses to vitamin D supplementation were noted across the seven trials, and some trials suggested that infants who are vitamin D deficient may respond differently and require higher doses of vitamin D to achieve serum 25(OH)D concentrations within the normal range.

Ottawa EPC report - Pregnant or lactating women.

There were six small RCTs of vitamin D supplementation in pregnant or lactating women. No randomized trials studied the effect of 400 IU vitamin D_3/d. Three trials used 1000 IU vitamin D_2/d and one trial used 1000 IU/d of vitamin D_3. Supplementation of vitamin D_2 1000-3600 IU/d and vitamin D_3 1000 IU/d resulted in significant increases in serum 25(OH)D concentrations in lactating mothers and in cord blood. One trial found that supplementation of lactating mothers with 1000 IU vitamin D_2/d during winter months did not significantly increase serum 25(OH)D concentrations in the infants.

Ottawa EPC report - Children and adolescents.

There were four trials that examined the effect of vitamin D on serum 25(OH)D concentrations in children or adolescents with doses ranging from 200 to 2000 IU of vitamin D_3 per day and 400 IU of vitamin D_2. There were consistent increases in serum 25(OH)D concentrations ranging from 8 nmol/L (200 IU/d), 16.5 (with 600 IU D_3/d) to 60 nmol/L (2000 IU of vitamin D_3/d).

Ottawa EPC report - Premenopausal women and younger men.

Ten small trials included premenopausal women and younger males. Three trials compared vitamin D_2 to vitamin D_3 in healthy young adults. Two of the three trials used RIA, and one used HPLC to measure serum 25(OH)D concentrations The doses of vitamin D_3 ranged from 600 to 10,000 IU/day and vitamin D_2 (4000 IU/d or 50,000 to 100,000 for single dose).

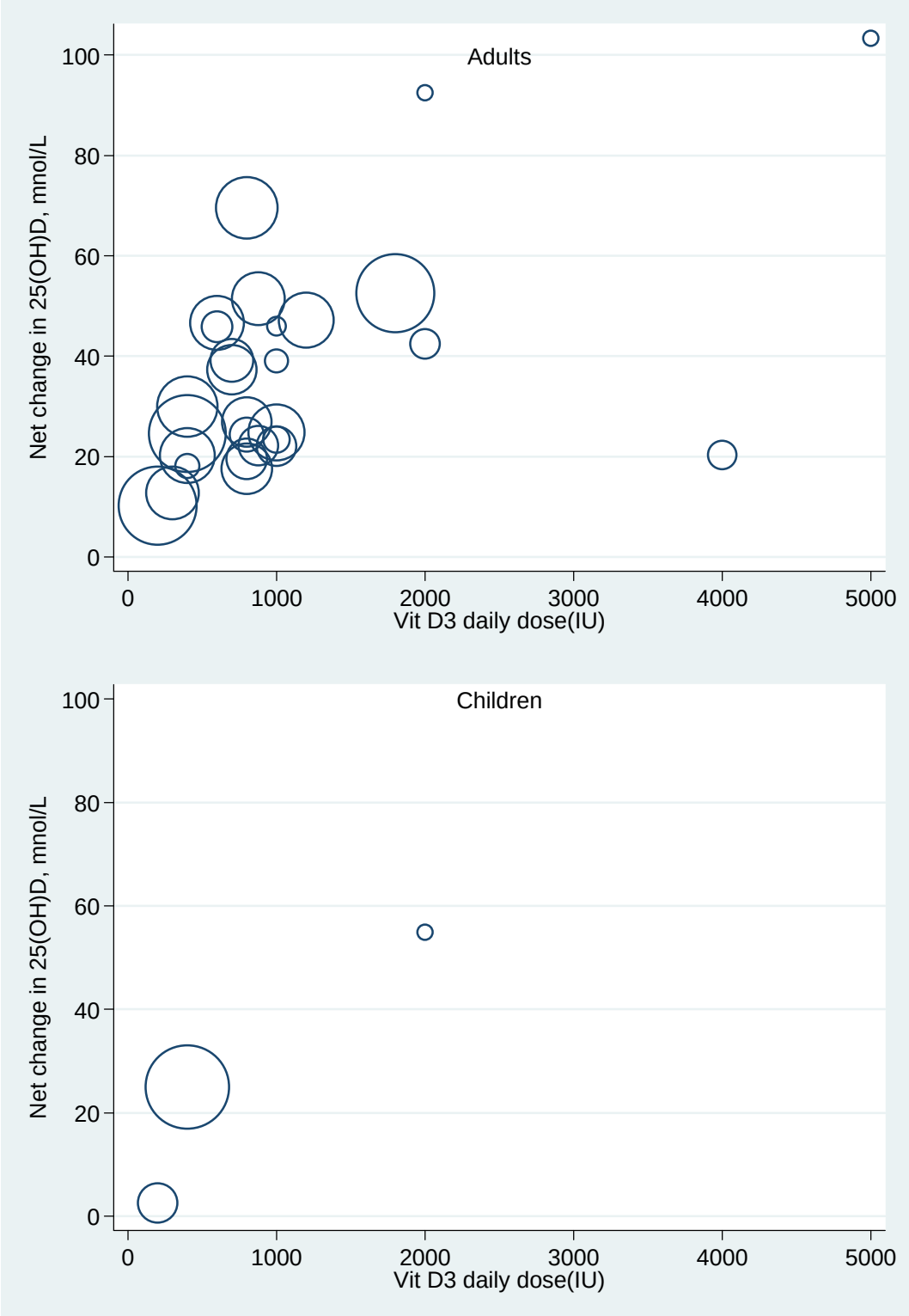
Three trials found that supplementation with vitamin D_2 and D_3 in healthy adults may have different effects on serum 25(OH)D concentrations. One trial compared 100,000 IU vitamin D_2 given orally versus injection and found a greater variability in response with the intramuscular preparation. There appeared to be dose-response effect in those trials that used multiple doses of vitamin D_3, although there were insufficient data to perform a meta-analysis.

Ottawa EPC report - Postmenopausal women and older men.

Forty-four trials were conducted exclusively in postmenopausal women and older men, with 14 of these in elderly populations living in long-term care or nursing homes. One trial enrolled only women in early menopause (n=129). Doses of vitamin D_3 ranged from 100 to 4000 IU/day and vitamin D_2 was 9000 IU/day. One trial was conducted in African American women.

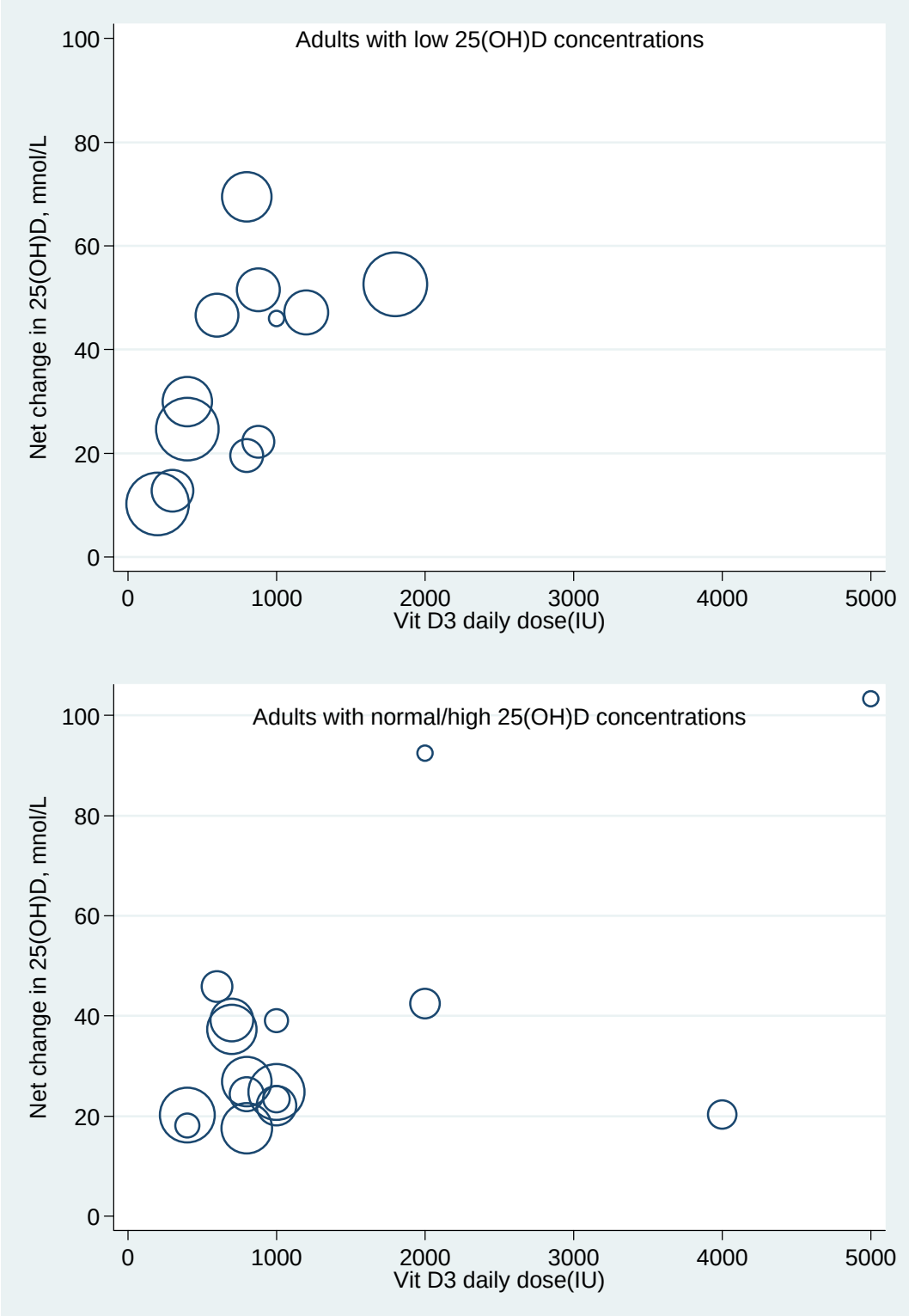
One trial found that wintertime declines in serum 25(OH)D concentrations were prevented with 500 IU vitamin D_3 per day. A dose response with increasing doses of vitamin D_3 was noted for serum 25(OH)D concentrations. There was variability in response to similar doses across trials that may have been due to differences in serum 25(OH)D assays or baseline 25(OH)D concentrations. Similarly, although some trials reported a greater response to vitamin D in populations that were vitamin D deficient at baseline compared to those who were not, there were insufficient data on which to base a definitive conclusion on this point.

Figure 23. Relationship between doses of Vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs



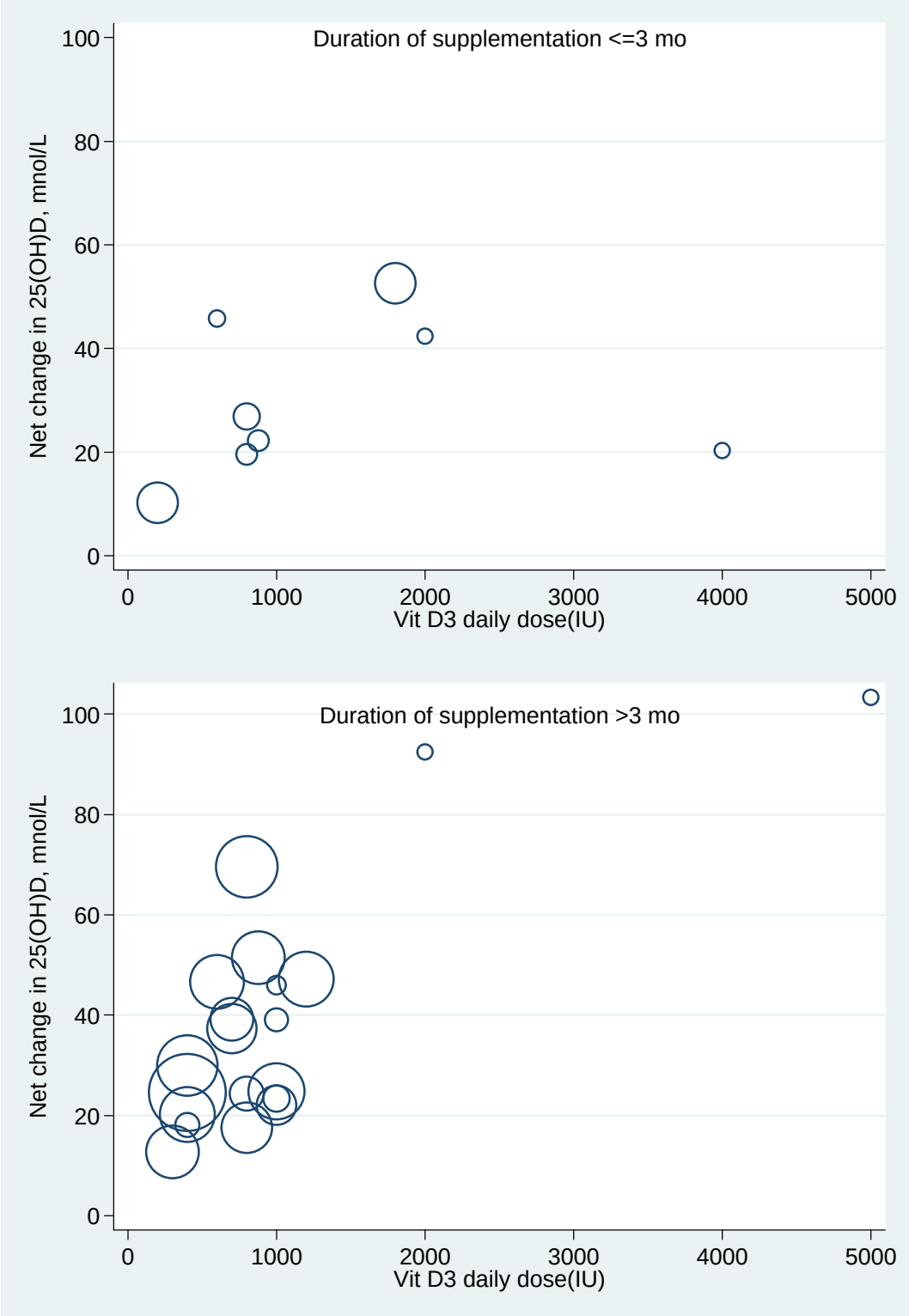
Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Figure 24. Relationship between doses of Vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults



Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Figure 25. Relationship between doses of Vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults



Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Table 106. The relationship between vitamin D_3 daily doses and changes in 25(OH)D concentrations in RCTs

Author	Year	Life stage	Base 25(OH)D, nmol/L	Vit D_3 dose (IU/d)	Ca dose (mg/d)	Duration (mo)	Vit D_3 ± Ca Group			Placebo or Ca Group		
							n	Mean change from baseline	SD	n	Mean change from baseline	SD
Bjorkman	2008[209]	71+	23	400	0	6	60	26.5	11.8	59	1.9	10.2
Bjorkman	2008[209]	71+	23	1200	0	6	63	49.1	19.5	59	1.9	10.2
Blum	2008[216]	71+	73	700	500[A]	12	132	48.5	35.3	125	9.3	21.5
Bunout	2006 [80]	71+	40	400	800[A]	9	46	33.4	14.3	46	3.5	10.0
Chapuy	1992 [217]	71+	36	800	1200	18	73	65.0	16.5	69	-4.5	13.5
Chel	2008[218]	71+	23	600	0	4	46	46.9	15.4	45	0.3	12.2
Deroisy	2002 [219]	71+	28	200	500[A]	3	50	14.7	10.0	50	4.5	10.0
Himmelstein	1990 [220]	71+	45	2000	0	1.5	15	39.7	15.7	15	-2.7	13.4
Kenny	2003 [221]	71+	62	1000	500[A]	6	29	22.3	10.1	31	-2.5	11.4
Krieg	1999 [222]	71+	29	880	500	24	34	36.5	14.0	38	-15.0	11.1
Pfeifer	2000 [223]	71+	25	880	1200[A]	2	74	40.5	27.0	74	18.3	20.9
Pfeifer	2001 [97]	71+	25	800	1200	2	73	39.2	22.4	72	19.7	23.8
Sorva	1991 [224]	71+	11	1000	1000	10	5	44.6	28.9	10	-1.4	2.3
Zhu	2008 [214]	71+	68	1000	1200[A]	60	29	36.2	27.5	34	-2.9	27.4
Barnes	2006 [225]	adults	52	600	1500[A]	2	12	38.6	15.1	15	-7.2	11.3
Bolton-Smith	2007 [213]	adults	60	400	100	24	50	12.0	15.1	56	-8.2	14.3
Dawson-Hughes	1997[226]	adults	74	700	500	36	145	35.2	32.6	167	-2.1	22.7
Harris	2002 [227]	adults	55	800	0	2	27	22.3	14.0	23	-4.6	6.3
Heaney	2003 [228]	adults	71	1000	0	5	16	12.0	16.0	16	-11.4	17.6
Heaney	2003 [228]	adults	71	5000	0	5	17	91.9	37.6	16	-11.4	17.6
Heikkinen	1998 [229]	adults	26	300	500[A]	12	18	9.4	10.9	18	-3.3	6.4
Honkanen	1990 [230]	adults	31	1800	1550	2.75	55	39.5	12.1	60	-13.1	9.2
Jensen	2002 [231]	adults	41	400	1450	36	33	34.6	23.2	33	16.5	28.2
Nelson	2009[232]	adults	62	800	0	12	55	35.3	23.2	31	10.9	16.9
Orwoll	1988 [233]	adults	58	1000	1000	12	46	25.0	19.1	46	3.0	19.1
Patel	2001 [234]	adults	72	800	0	12	35	8.4	13.1	35	-9.2	12.8
Riis	1984 [235]	adults	41	2000	500	12	8	87.5	14.1	7	-5.0	23.8

continued

Author	Year	Life stage	Base 25(OH)D, nmol/L	Vit D_3 dose (IU/d)	Ca dose (mg/d)	Duration (mo)	Vit D_3 ± Ca Group			Placebo or Ca Group		
							n	Mean change from baseline	SD	n	Mean change from baseline	SD
Trang	1998 [236]	adults	42	4000	0	0.5	24	23.3	17.5	24	3.0	19.8
Chan	1982 [237]	children	43	400	0	6	30	22.5	6.6	30	-2.5	6.6
El-Hajj (Fuleihan)	2006 [35]	children	35	200	0	12	58	7.5	19.8	55	5.0	18.8
El-Hajj (Fuleihan)	2006 [35]	children	35	2000	0	12	55	59.9	67.1	55	5.0	18.8

[A] Calcium supplement was given to all patients

The format of this table has been slightly modifies to fit each RCT in one line.

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. In brief, we did not find vitamin D and/or calcium associated with an increased risk of mortality. For cancer risk, there were some observational studies reporting high calcium intake may be associated with an increased risk of prostate cancer (see "Prostate cancer" in "Calcium and cancer" section). We did not identify any studies on soft tissue calcification and tolerable upper intake levels.

Renal Outcomes

The WHI trial on women aged 50 to 79 years, examined the effect of vitamin D_3 400 IU (the Recommended Dietary Allowance for women aged 50 to 70 years and below the 600 IU recommended intake for women > 70 years) in combination with 1000 mg calcium carbonate versus placebo and found an increase in the risk of renal stones (Hazard Ratio 1.17 95 percent CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.[71] It should be noted that women in both groups were allowed to take additional vitamin D supplements up to 600 IU and later 1000 IU per day and calcium supplements up to 1000 mg per day. The baseline total calcium intakes (from foods and supplements) were high: 34 percent consumed less than 800 mg/d, 26 percent consumed 800 to 1200 mg/d, and 40 percent consumed more than 1200 mg/d. A prior publication from WHI trial provided the same data on the risk of renal stones was also included in the Ottawa EPC report.

No studies were identified that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

Adverse Events Reported in RCTs.

The 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 this report, 47 did not report information on adverse events.

Five RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods.[35,51,227,238,239] Of these, one RCT administered combination of vitamin D_2 (1600 or 3600 IU/d) and vitamin D_3 (400 IU/d) supplements for 3 months, two RCTs administered vitamin D supplements (type of vitamin D not reported) with doses ranging from 200 to 2000 IU/d for 3 weeks or 1 year, one RCT used high-dose intermittent vitamin D_3 supplement (120,000 IU sachets given 3 times, every 2 weeks, for 6 weeks), and one RCT administered 1200 IU/d vitamin D_2 supplement for 5 years.

Eleven RCTs reported at least one adverse event (Table 107). 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 5714 IU/d vitamin D_3 or ranged from 5000 to 10,000 vitamin D_2) and/or calcium supplementations (doses ranged from 200 to 1500 mg/d) reported few

cases of gastrointestinal disruption such as constipation, diarrhea, upset stomach, musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, renal calculi and craniotabes. One RCT reported some adverse events that required hospital admission, including retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack (all 3 cases in vitamin D 400 IU/d plus exercise training group) and one case of acute cholecystitis (in calcium, vitamin D plus exercise training group).[80] Another RCT reported that "there were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke)" (actual data not provided), and one participant died during the study.[98] However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study. Also described earlier in the "Renal outcomes" section, the WHI trial examined the effect of vitamin D_3 400 IU in combination with 1000 mg calcium carbonate versus placebo and found an increase in the risk of renal stones (Hazard Ratio 1.17 95 percent CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.[71]

Ottawa EPC report:

A total of 22 trials reported data on toxicity-related outcomes, 21 of which used doses above 400 IU/d. Toxicity results from trials with intakes of vitamin D above current reference intakes varied and this may have been related to different doses, baseline characteristics of populations or exposure times. Most trials excluded subjects with renal insufficiency or hypercalcemia, were of small sample sizes and had short durations of exposure to vitamin D. Event rates were low across trials in both the treatment and placebo arms.

Table 107. Adverse events reported in RCTs

Author Year	N enrolled	Vit D dose (IU/d)	Ca dose (mg/d)	Duration	Adverse Event data (n=case#)
Yamamoto 1995 [117]	471	0	1000	6 mo	Comparing calcium group to the placebo group, excessive gas and bloating were more frequently reported by white women at 3 months and by whites, in general, at 6 months, and white men reported more loose stools at 6 months.
Moschonis 2006 [215]	112	300 D_3	600 or 1200	12 mo	Bloating, constipation and intestinal discomfort apparently related to the calcium supplement
Bunout 2006 [80]	96	400	800	9 mo	Adverse events that required hospital admission: Vit D plus exercise training group (n=3): retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack. Calcium, Vit D plus exercise training group (n=1): acute cholecystitis
Wactawski-Wende 2006 [71]	36282	400	1000	7 y	The WHI trial found an increase in the risk of renal stones (Hazard Ratio 1.17 95% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.
Burleigh 2007 [81]	205	800 D_3	1200	Median 1 mo	Hypercalcemia (n=2)
Lappe 2008 [208]	5201	800	200	8 wks	GI disruption such as constipation, diarrhea, upset stomach (4%), and musculoskeletal soreness (0.9%)
Brooke 1980 [34]	126	1000	0	3rd trimester only	Vit D group (craniotabes, n=2), placebo group (hypocalcemia, n=5; craniotabes, n=6)
Lappe 2007 [52]	1180	1000 D_3	1400-1500	4 y	Renal calculi in placebo (n=1), renal calculi in calcium only (n=3), renal calculi in calcium plus vit D (n=1)
Mastaglia 2006 [240]	65	5000 or 10,000 D_2	500	3 mo	Hypercalciuria (n=1) in control group
Zhu2008[98]	256	1000 D_2	1200	12 mo	There were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke). There were 8 and 5 adverse events in vitamin D and the control groups, respectively. One participant in the vitamin D group had mild asymptomatic hypercalcemia one occasion. No case of renal calculus was reported. 1 participant was deceased during the study.
Sneve 2008[50]	445	Group 1: 2 capsules of vitamin D_3 each 20,000 IU taken twice a week (Monday and Thursday): ~5714 IU/d Group 2: 1 capsules of vitamin D_3 each 20,000 IU taken twice a week (Monday and Thursday): ~2857 IU/d	500	12 mo	Primary hyperparathyroidism (n=2), increase in serum calcium to 2.62 mmol/L (n=1), transient increases in serum calcium > 2.59 mmol/L (n=4). 317 other adverse events were recorded, most of them related to GI discomfort. There were no significant differences between the treatment groups regarding adverse events.

Chapter 4. Discussion

This evidence report on vitamin D and calcium in relation to health outcomes was prepared for consideration by the Committee on Dietary Reference Intakes for Vitamin D and Calcium at the request of AHRQ on behalf of the various sponsors. This report does not make nor was it intended to make recommendations for DRI values concerning vitamin D or calcium. Responsibility for setting DRI values lies with the Committee. Evidence from systematic reviews is one of several types of information available to the Committee for use in its deliberations to establish DRI values. This is the first time that an independent systematic review is being commissioned to support the DRI process. Thus, it is important for users of this report to fully appreciate the nuances of the methodologies employed, as well as the strengths and limitations of this approach. In particular, it should be noted that total vitamin D exposure was not evaluated in this report because there is no valid method to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure and it is also the TEP's consensus that vitamin D intake, as estimated by current food frequency questionnaires, is too inaccurate to be of value.

For this report, we identified 165 primary articles that met the eligibility criteria established by the TEP. In addition, we included 11 published systematic reviews that incorporated over 200 additional primary articles. Despite the relatively large number of studies included, with the following few exceptions, it is difficult to make any substantive and concise statements on the basis of the available evidence concerning the association of serum 25(OH)D concentration, supplemental vitamin D, dietary calcium intake, or the combination of both nutrients with the various health outcomes. It proved challenging because many of the studies contained substantial heterogeneity and their findings were inconsistent for the health outcomes examined.

In general, among RCTs of hypertensive adults, calcium supplementation (400 to 2000 mg/d) lowered systolic, but not diastolic, blood pressure by a small but statistically significant amount (2 to 4 mm Hg).

For body weight, despite a wide range of calcium intakes (from supplements or from dairy and nondairy sources) across the calcium trials, the RCTs were fairly consistent in finding no significant effect of increased calcium intake on body weight.

For growth, a meta-analysis of 17 RCTs 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.

For bone health, one well-conducted systematic review of RCTs found that vitamin D_3 (up to 800 IU/d) plus calcium (~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.

For breast cancer, subgroup analyses in four cohort studies consistently found that calcium intake in the range of 780 to 1750 mg/d in premenopausal women was associated with a decreased risk for breast cancer. However, no RCTs of calcium supplementation to prevent breast cancer in premenopausal women have been published. In contrast, cohort studies of postmenopausal women are consistent in showing no association of calcium intake with the risk of breast cancer.

For prostate cancer, three of four cohort studies found significant associations between higher calcium intake (>1500 or >2000 mg/day) and increased risk of prostate cancer, compared to men consuming lower amount of calcium (500-1000 mg/day).

For cardiovascular events, a cohort study and a nested case-control study 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 an RCT found no effect of supplementation and studies of specific cardiovascular events were too sparse to reach conclusions. 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/day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the US, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1000 mg.

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectum, 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.

Strengths of This Report

The strengths of this report lie in the wide range of topics covered, critical appraisal, detailed documentation, transparent methods to assess the scientific literature, and an unbiased selection of studies. A team of evidence-based methodologists not previously directly involved in research related to vitamin D and calcium worked with nutrient experts to refine the key questions (initially defined by AHRQ with input from various sponsors), analytic framework, and review criteria for the systematic review. After defining the questions and eligibility criteria with input from content experts and the sponsoring agencies, the Tufts EPC reviewed the published evidence on the topic. The intent was to perform a thorough and unbiased systematic review of the literature base on available evidence as defined by prespecified criteria. Once the review process began, input from experts in the field was sought to clarify technical questions during the literature review process. These individuals did not participate in study selection or detailed data extraction from the included studies nor were any members serving on the IOM committee on vitamin D and calcium involved in the review of this document. A quality rating as detailed in Chapter 2 (Methods section) was assigned for each primary study and systematic review, and incorporated into the data summaries section of the report. On the basis of this work, a sound foundation has been created which will facilitate rapid and efficient future updates as needed.

Details concerning the process of question formulation, selection of health outcomes of interest, justification for study selection criteria, methods used for critical appraisals of studies and quality rating, and summary of results are described fully in the Methods chapter. This approach is critical to the establishment of a transparent and reproducible process. Furthermore, important variables that affect vitamin D status such as life stages, latitude of the study locale, background diet and skin pigmentation are documented in this review.

This evidence report was carried out under the AHRQ EPC program, which has a 12-year history of producing over 175 evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continuously refine approaches to conducting systematic reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. In addition, the Tufts EPC has conducted a number of nutrition-related evidence reports[19-22,241], as well as

conducted the mock exercise on vitamin A panel.[3] This report drew on these experiences, the expertise of the TEP, and the support of federal agencies.

DRI and the Literature on Vitamin D and Calcium

It should be emphasized that none of the studies reviewed were designed to address issues specifically relevant for establishing DRI values (i.e., to ascertain the optimal dose in a particular life stage to promote growth and tissue maintenance, and prevent chronic disease throughout the lifecycle). In general, the studies did not enroll subjects with ages that could be easily mapped to specific life stages as defined within the DRI framework (with the exception of postmenopausal women and pregnant or lactating women) and did not evaluate health outcomes on the basis of what doses will lower risk for a particular disease in prespecified life stages. Therefore, data will need to be extrapolated from these studies to craft a set of DRI values for vitamin D and calcium. This extrapolation may prove challenging.

Certain issues concerning the studies of vitamin D must be noted. As mentioned previously, it is difficult to evaluate nutritional adequacy because there are no methods currently available to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure on an individual or group level. In addition, it is generally accepted that estimating intake by dietary assessments is not a valid indicator of vitamin D status, because there are limitations in the completeness of nutrient databases for both food and dietary supplements vitamin D content and the rapidly changing landscape of vitamin D food fortification has not yet been captured in either instruments used to assess intake and the databases used to analyze the data. For example, vitamin D values are available for only about 600 out of 1400 foods in the USDA National Nutrient Database for Standard Reference (http://www.ars.usda.gov/nutrientdata) and notably missing are foods recently fortified with vitamin D.[25] Given the recent trend towards increased nutrient fortification of the North American food supply, the lag in updating food composition tables, and the inability to distinguish between fortified and unfortified foods when using most dietary assessment tools, it is difficult to accurately estimate dietary intakes of vitamin D, especially for a given year. Shifts in methodological approaches to measure serum 25(OH)D concentrations, the heterogeneous nature of the data available with respect to study locations (i.e., latitude) and times during the year (i.e., season) hamper our ability to succinctly summarize dose-response relationships. We did not perform a dose-response meta-analysis of the relationship between serum 25(OH)D concentrations and health outcomes because limited and inconsistent data would result in a meta-analysis that is difficult to interpret and results that may be misleading. Furthermore, many of the large cohorts analyzed for associations of vitamin D with health outcomes enrolled mostly white participants aged approximately 40 to 70 years old and much of the data on intake dose-response and serum 25(OH)D concentration were derived from studies designed to measure bone health in postmenopausal women. These factors limit the applicability of the findings to other life stages and other racial groups.

Unlike serum 25(OH)D concentrations for vitamin D, there is no equivalent serum biomarker to indicate calcium status. Relying on dietary assessment to gauge calcium intake is limited by the confounding effect of vitamin D status on the efficiency of calcium absorption and uncertainties in the calcium content of many foods due to the recent trend in nutrient fortification of food, limited ability of current dietary assessment tools to distinguish among fortified and unfortified foods and the lag in updating nutrient databases with current nutrient information.

Limitations of our Methodological Approach

The number of potentially relevant (English language articles on humans and not reviews) vitamin D studies indexed in MEDLINE is very large (~15,000) and the number of calcium studies is even larger (~110,000). Without unlimited time and resources, the systematic review conducted in this report had to focus on selected key questions predefined by our federal sponsors with input from the IOM, and capitalize on existing systematic reviews. Using previous systematic reviews risks propagating deficiencies and errors[242] introduced in those reviews (e.g., errors in data abstraction, flawed assumptions in quantitative synthesis). Although we have assessed the quality of these systematic reviews using AMSTAR[26] checklist, we cannot reliably know the validity of the reported summary data without knowing the details of the primary studies. It should also be stressed that a well-performed systematic review does not necessarily imply that the body of evidence for a particular outcome of interest is of high quality. While some systematic reviews assessed the quality of the individual studies, the methods used varied. Any systematic review is limited by the quality of the primary studies included in the review. Unless the methods used to assess the quality of the primary studies is transparent and the details made available for examination, it would be difficult to reliably determine the validity of the conclusions. Also, relying on existing systematic reviews alone could have potentially precluded us from identifying all relevant studies because those systematic reviews might have addressed somewhat different questions and had a different scope from this review. For example, for growth outcome in children, we principally relied on the findings from a meta-analysis of RCTs of calcium originally designed to evaluate bone density outcomes. If there were RCTs of calcium intake specifically designed to measure growth outcomes such as weight and height gain, but not bone density, then those studies would not have been identified. In addition, as per the task order from AHRQ, we relied on the Ottawa report for bone health outcomes and we did not examine specific studies included in that report. As a consequence, if those studies had reported other (than bone health) outcomes that were of interest, those studies would not have been included in this review.

As there is no consensus on how to assess the quality of the nutrition observational studies, we created a quality checklist based on a newly published reporting standard for observational studies[32] and nutrition reporting items that we believe should be considered in quality assessment. This checklist, however, has not been calibrated and the intra- and interrater variability have not been assessed. We should also remind the readers that impeccable study reporting does not equate study validity. However, transparent, comprehensive, and accurate reporting does help in evaluating a study's validity.

Also, studies on vitamin D and calcium were not specifically targeted at life stages (except for children, pregnant, and postmenopausal women) specified for the determination of DRI. We, therefore, were unable to structure our report strictly according to prespecified life stages. When a study enrolled populations that spanned across multiple life stages, we provided our best estimates as to which life stage(s) the study's findings would be of most relevance.

Comments on the Observational Studies

All the included observational studies were designed to generate hypotheses of potential associations of multiple factors with vitamin D or calcium. Therefore, a finding of a significant association in these studies, after exploratory analyses, should not be considered equivalent to

the result of studies that were designed to confirm this relationship. Many of the nested case-control studies typically excluded a substantial portion of participants (some as high as 60 to 70 percent) in the original cohorts because blood samples, or completed dietary questionnaires were not available. How this selection bias would affect the reported association is unclear. In addition, several of the studies might have suffered from outcome misclassification; for example, when cancer cases were identified from registries without histopathology verification. The effect of outcome misclassification is unpredictable. Furthermore, many of the studies did not report a power calculation. Even though many of the studies included cohorts with relatively large numbers of subjects (tens of thousands), it is plausible that, in fact, the included studies may have been underpowered to detect the true effect sizes. If that were the case, the significant effect reported may, in fact, be spurious. Furthermore, many of the reported effect sizes were small to moderate (with OR ranged from 1.03 to 2.0). When the effect size is small, the possibility of residual confounding by unmeasured variables must be considered.

Sources of Heterogeneity and Potential Biases

As have been mentioned previously, most of the findings reported in this review were inconsistent for each of the outcomes of interest. Many studies showed substantial heterogeneity. Some studies adjusted the serum 25(OH)D concentration by season of serum collection, some did not. While the majority of the studies used some forms of RIA to measure the serum 25(OH)D concentration, a minority used competitive protein-binding assay. Some studies reported a substantial proportion of the frozen serums were accidentally thawed and limited the analyses that could be performed. It is unclear how this would alter the overall results. Many studies suffered from potentially inadequate outcome ascertainment (e.g., reliance on self-reported calcium intake and hypertension diagnosis). Time between measurement of serum 25(OH)D concentration and the diagnosis of interest varied. For prostate and colorectal cancer, it ranged from 1 to more than 16 years. Factors potentially relevant to the outcomes of interest like family history (in colorectal cancer) were not consistently reported and accounted for in the studies. Also, the blinding of case assessors to the risk factor of interest (e.g., serum 25(OH)D concentrations) as well as that of investigators who measured the risk factor *per se* to outcomes were rarely reported.

For studies on calcium supplementation, intake compliance, information on the bioavailability of the calcium source, the role of background sun exposure, and associated vitamin D effects were not consistently available across all studies. Thus, it is difficult to interpret those findings on an absolute level and among studies.

Finally, all systematic reviews, including this report, may suffer from potential publication and reporting biases since currently there is no reliable way to detect and correct these biases. However, there is an underlying suspicion of publication bias against studies having either null or negative outcomes and reporting bias toward “significant” outcomes in the literature.[243,244] Thus, it is important to consider these biases when reviewing the overall findings of any systematic review.

Vitamin D Intake and Response in Serum 25(OH)D Concentration

The findings of this review on the association between vitamin D intake dose and change in serum 25(OH)D concentration was primarily derived from RCTs reviewed in a systematic review of bone health in postmenopausal women. This limits the applicability of the findings to

other life stages. Though, we did not find any reason to consider these trials to be biased, they are nonetheless an arbitrary sample of all studies that have reported the association between vitamin D intake dose and change in serum 25(OH)D concentration. We did not perform a quantitative synthesis (e.g., meta-regression) to examine the relationship between vitamin D intake dose and serum 25(OH)D concentration due to the heterogeneity across studies. Studies had varied compliance rates in the vitamin D intake; limited or no adjustment for skin pigmentations, calcium intake, or background sun exposure; different vitamin D assay methodologies and measurement (both intra- and interassay) variability. All these factors increase the heterogeneity and limit the usefulness of an overall summary estimate for an intake dose response in serum 25(OH)D concentration. Nonetheless, overall, there appeared to be a trend for higher vitamin D supplementation dose resulting in higher net change in serum 25(OH)D concentration.

Considerations for Future DRI Committees

Formulating the appropriate key questions is the most important aspect of conducting a systematic review to ensure the final product will meet the intended purpose. Ideally, this should be an iterative process involving the sponsors, EPC, TEP and targeted end-users. The questions should be reviewed and potentially refined once the "state" of the literature has been systematically appraised, with the understanding that any modifications to the key questions after the review process has started will likely extend the literature review and synthesis processes. In addition, developing relevant study selection criteria for the systematic review is critical to finding pertinent data to answer the key questions; the TEP should be engaged early in this process. Crafting a framework of the entire review process depicting the explicit roles of the sponsors, TEP, and targeted end-users could also be helpful for future reviews.

While the process of conducting the actual systematic review of a nutrient or group of nutrients on an agreed upon set of key questions concerning specific health outcomes is carefully laid out and could be replicated without undue difficulty, the process of selecting which health outcomes would be important for inclusion in a systematic review could not be easily replicated. The health outcomes selected were decided after much deliberation by the TEP with input from the various partners. As the nature of the deliberation hinged much on the expertise reflected by the particular composition of the TEP, it is conceivable that a different TEP composed of members with different expertise may have recommended a different set of health outcomes for inclusion. To minimize this variability, an a priori designed set of instructions to weigh each outcome (taking into account such factors like population attributable risk, morbidity, and others) for possible inclusion would be valuable.

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Abbreviations

25(OH)D	25-hydroxyvitamin D
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessment of multiple systematic reviews
Anthrop	Anthropometric measures
ASA	Acetyl-salicylic acid (aspirin)
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BCDDP	Breast Cancer Detection Demonstration Project
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body Mass Index
Ca	Calcium
CABG	Coronary artery bypass graft
CeVD	Cerebrovascular disease
CHD	Coronary heart disease
CHD	Coronary Heart Disease
CI	Confidence Interval
CIFOS	Calcium Intake Fracture Outcome Study
CONSORT	Consolidated Standards of Reporting Trials
CPBA	Competitive protein binding assay
CPEP	Calcium for Prevention of Preeclampsia Trial
CPP	Calcium Polyp Prevention Study
CPS	Cancer Prevention Study
CRC	Colorectal cancer
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
Demograph	Demographics
DM	Diabetes Mellitus
DRI	Dietary Reference Intake
Dx	Diagnosis
EAR	Estimated average requirement
EPC	Evidence-based Practice Center

FFQ	Food frequency questionnaire
FNB	Food and Nutrition Board
FOS	Framingham Offspring Study
FREE	Fracture Risk Epidemiology in the Elderly
HAH	Harvard Alumni Health Study
HbC	Hemoglobin C disease
HPFS	Health Professionals Follow-up Study
HPLC	High pressure liquid chromatography
HR	Hazard ratio
ht	Height
HT	Hormone (replacement) therapy
HTN	Hypertension
IHD	Ischemic heart disease
IOM	Institute of Medicine
Iowa WHS	Iowa Women's Health Study
IQR	Interquartile range
IU	International unit
Japan CC	Japan Collaborative Cohort
Japan PHC	Japan Public Health Center study
Kupio ORFPS	Kupio Osteoporosis Risk Factor and Prevention Study
MCS	Multiethnic Cohort Study, Hawaii, California
MI	Myocardial infarction
mil	Million
mo	Months(s)
N	Number of subjects
n	Number of subjects had event(s)
NA	Not applicable
nd	No data
NHANES	National Health and Nutrition Examination Survey
NHEFS	NHANES I Epidemiologic Follow-up Study
NHS	Nurses' Health Study

NIH	National Institutes of Health
NIH-AARP	National Institutes of Health – American Association of Retired Persons
NPC	Nutrition Prevention of Cancer trial
NS	Not significant
ODS	Office of Dietary Supplements
OR	Odds Ratio
PAHSG	Princess Anne Hospital Study Group, UK
PCI	Percutaneous coronary intervention
PHS	Physicians' Health Study
PI(E)CO	Population, Intervention (or Exposure), Comparison and Outcome
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PMID	PubMed (unique) identifier
PSA	Prostate specific antigen
PTH	Parathyroid hormone
RCT	Randomized-controlled trial
RDA	Recommended Dietary Allowance
RIA	Radioimmunoassay
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Subgp	Subgroup
Suppl	Supplement(s)
TEP	Technical Expert Panel
TIA	Transient ischemic attach
TOHP	Trials of Hypertension Prevention
TOO	Task order officer
UK	United Kingdom
UL	Tolerable upper intake levels
US	United States
USDA	United States Department of Agriculture

UV	Ultraviolet rays
Vit	Vitamin
WCC	Washington County Cohort
WHI	Women's Health Initiative
WHS	Women’s Health Study
wk	week(s)
WMD	Weighted mean difference
wt	Weight
y	Year(s)

Latitudes of Selected Cities

Latitude	Western Hemisphere	Eastern Hemisphere
64° N	Reykjavik, Iceland Nome, Alaska	
60-61° N	Anchorage, Alaska	Oslo, Norway
56° N		Copenhagen, Denmark
52° N		Berlin, Germany Amsterdam, Netherlands
51° N	Calgary, Alberta	London, England
49° N	Vancouver, British Columbia	Paris, France
48° N	Seattle, Washington	Munich, Germany
47° N	Quebec City, Quebec Bismarck, North Dakota	Zurich, Switzerland
45° N	Ottawa, Ontario Minneapolis, Minnesota	Milan, Italy
44° N	Toronto, Ontario Portland, Maine	
42° N	Boston, Massachusetts Chicago, Illinois	Rome, Italy
41° N	New York, New York Salt Lake City, Utah	Barcelona, Spain
40° N	Philadelphia, Pennsylvania Columbus, Ohio Washington, DC	Madrid, Spain Beijing, China
39° N	St Louis, Missouri Sacramento, California Louisville, Kentucky	
38° N	Wichita, Kansas San Francisco, California	Athens, Greece
36° N	Raleigh, North Carolina Las Vegas, Nevada	Tokyo, Japan
34° N	Columbia, South Carolina Los Angeles, California	Fez, Morocco
33° N	Dallas, Texas	
30° N	New Orleans, Louisiana	Cairo, Egypt
29° N	San Antonio, Texas	New Delhi, India
26° N	Miami, Florida	
22° N		Hong Kong, China
21° N	Honolulu, Hawaii	
19° N	Mexico City, Mexico	Mumbai (Bombay), India
15° N	Guatemala City, Guatemala	Manila, Philippines
10° N	Caracas, Venezuela	
4° N	Bogota, Columbia	
1° N		Singapore
12° S	Lima, Peru	
23° S	Rio de Janeiro, Brazil	
26° S		Johannesburg, South Africa
34° S		Sydney, Australia Cape Town, South Africa
35° S	Buenos Aires, Argentina	
37° S		Auckland, New Zealand
38° S		Melbourne, Australia
41° S		Wellington, New Zealand

Appendix A. Search strategy for primary studies

a. Overall Search Strategy for Outcomes of Estimated Average Requirements

Database: Ovid MEDLINE(R), CCTR (1969 to April 2009)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
4. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/
9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol$.tw.
12. Cholecalciferol/
13. Cholecalciferol$.tw.
14. calciferol.tw.
15. or/1-14
16. exp Calcium/
17. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
18. exp Calcium, Dietary/
19. calcium.tw.
20. or/16-19
21. (ANIMALS not HUMAN).sh.
22. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
23. 15 or 20
24. 23 not 21
25. 24 not 22
26. limit 25 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or "review")
27. 25 not 26
28. limit 27 to english language
29. randomized controlled trial.pt.

30. controlled clinical trial.pt.
31. randomized controlled trials/
32. Random Allocation/
33. Double-blind Method/
34. Single-Blind Method/
35. clinical trial.pt.
36. Clinical Trials.mp. or exp Clinical Trials/
37. (clinic$ adj25 trial$).tw.
38. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
39. Placebos/
40. placebo$.tw.
41. random$.tw.
42. trial$.tw.
43. (latin adj square).tw.
44. Comparative Study.tw.
45. exp Evaluation studies/
46. Follow-Up Studies/
47. Prospective Studies/
48. (control$ or prospectiv$ or volunteer$).tw.
49. Cross-Over Studies/
50. or/29-49
51. 50 and 28
52. 28 not 51
53. limit 51 to yr="1969-2008"
54. limit 52 to yr="1969-2008"
55. 53 not ("200810$" or "200811$" or "200812$").ed.
56. 54 not ("200810$" or "200811$" or "200812$").ed.
57. 55 or 56
58. exp Vitamin D/
59. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
60. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
61. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
62. 25-hydroxycholecalciferol.tw.
63. 25-hydroxyergocalciferol.tw.
64. calcidiol.tw.
65. Calcifediol/
66. (vit adj (d or d2 or d3)).mp.

67. Ergocalciferols/
68. Ergocalciferol$.tw.
69. Cholecalciferol/
70. Cholecalciferol$.tw.
71. calciferol.tw.
72. or/58-71
73. exp Calcium/
74. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
75. exp Calcium, Dietary/
76. calcium.tw.
77. or/73-76
78. (ANIMALS not HUMAN).sh.
79. (ANIMALS not HUMAN).sh.
80. 72 or 77
81. 80 not 78
82. 81 not 79
83. limit 82 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or "review")
84. 82 not 83
85. limit 84 to english language
86. randomized controlled trial.pt.
87. controlled clinical trial.pt.
88. randomized controlled trials/
89. Random Allocation/
90. Double-blind Method/
91. Single-Blind Method/
92. clinical trial.pt.
93. Clinical Trials.mp. or exp Clinical Trials/
94. (clinic$ adj25 trial$).tw.
95. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
96. Placebos/
97. placebo$.tw.
98. random$.tw.
99. trial$.tw.
100. (latin adj square).tw.
101. Comparative Study.tw.

102. exp Evaluation studies/
103. Follow-Up Studies/
104. Prospective Studies/
105. (control$ or prospectiv$ or volunteer$).tw.
106. Cross-Over Studies/
107. or/86-106
108. 107 and 85
109. 85 not 108
110. limit 108 to yr="1969-2008"
111. limit 109 to yr="1969-2008"
112. 110 not ("200810$" or "200811$" or "200812$").ed.
113. 111 not ("200810$" or "200811$" or "200812$").ed.
114. 112 or 113
115. verapamil.mp. or 52-53-9.rn.
116. nifedipine.mp. or 21829-25-4.rn.
117. diltiazem.mp. or 42399-41-7.rn.
118. Azelnidipine.mp. or 123524-52-7.rn.
119. nicardipine.mp. or 55985-32-5.rn.
120. felodipine.mp. or 72509-76-3.rn.
121. mepirodipine.mp. or 104713-75-9.rn.
122. Amlodipine.mp. or 88150-42-9.rn.
123. isradipine.mp. or 75695-93-1.rn.
124. bepridil.mp. or 64706-54-3.rn.
125. gallopamil.mp. or 16662-47-8.rn.
126. aranidipine.mp. or 86780-90-7.rn.
127. nitrendipine.mp. or 39562-70-4.rn.
128. Barnidipine.mp.
129. benidipine.mp. or 105979-17-7.rn.
130. Cilnidipine.mp. or 132203-70-4.rn.
131. clevidipine.mp.
132. efonidipine.mp. or 111011-53-1.rn.
133. Lacidipine.mp. or 103890-78-4.rn.
134. Lercanidipine.mp. or 100427-26-7.rn.
135. Manidipine.mp. or 89226-50-6.rn.
136. Nilvadipine.mp. or 75530-68-6.rn.
137. Nimodipine.mp. or 66085-59-4.rn.
138. Nisoldipine.mp. or 63675-72-9.rn.
139. Pranidipine.mp. or 99522-79-9.rn.

140. ((calcium or Ca) adj3 channel$).mp.

141. ((calcium or Ca) adj3 agonist$).mp.

142. (intracellular adj2 (calcium or Ca)).mp.

143. or/115-142

144. weight loss.mp. or exp Weight Loss/

145. body mass index.mp. or exp Body Mass Index/ or exp Body Mass/ or body mass.mp. or exp body weight/ or body weight.mp.

146. 144 or 145

147. obesity.mp. or exp OBESITY/pc, di, ep, et

148. or/144-147

149. limit 148 to ("all infant (birth to 23 months)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)")

150. limit 149 to ("all adult (19 plus years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)" or "adult (19 to 44 years)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

151. 149 not 150

152. 148 not 151

153. exp Body Height/

154. exp body size/

155. growth velocity.af.

156. growth retardation.af.

157. growth delay.af.

158. growth restriction.af.

159. (height adj6 restrict$).af.

160. linear velocity.af.

161. (height adj6 delay).af.

162. length delay.af.

163. (length adj6 retardation).af.

164. or/153-163

165. limit 164 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")

166. 164 not 165

167. limit 166 to ("all adult (19 plus years)" or "adult (19 to 44 years)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

168. 164 not 167

169. Bone Density/

170. exp Osteoporosis/

171. ((bone$ or plate$) adj3 mineral$).tw.

172. (bone adj2 (loss or turnover or densi$)).tw.

173. (Skelet$ adj2 (mineral$ or development$)).tw.
174. mineralization defect$.tw.
175. Mineral$ content$.tw.
176. BMC.tw.
177. Osteoporo$.tw.
178. Osteomalac$.tw.
179. Osteopath$.tw.
180. Bone Development/
181. Osteogenesis/
182. fracture$.tw.
183. Accidental Falls/
184. falls.tw.
185. exp "Bone and Bones"/
186. or/169-185
187. Rickets/
188. rachitis.tw.
189. rickets.tw.
190. or/187-189
191. tooth loss.mp. or exp Tooth Loss/
192. 190 or 186 or 191
193. limit 192 to yr="2006-2008"
194. exp Cardiovascular Diseases/pc, di, ep, et
195. Cardi$.mp.
196. 195
197. Coronary.mp.
198. heart disease$.mp.
199. Myocardial infarct$.mp.
200. exp Cerebrovascular Accident/
201. stroke.tw.
202. Transient Ischemic Attack.tw.
203. exp Ischemia/
204. cardioprotect$.mp.
205. Pulmonary Embol$.tw.
206. Heart failure$.tw.
207. (embol$ or thromb$).tw.
208. exp Peripheral Vascular Diseases/ or peripheral artery disease.mp.
209. arterial occlusive diseases/
210. or/194-209

211. limit 210 to "all adult (19 plus years)"
212. exp hypertension/pc, di, ep, et
213. exp hypertension, renal/
214. hypertens$.af.
215. high blood pressure.af.
216. (eleva$ adj2 blood pressure).tw.
217. systolic blood pressure/
218. diastolic blood pressure/
219. mean arterial pressure/
220. or/212-219
221. limit 220 to "all adult (19 plus years)"
222. exp Neoplasms/dh, pc, et, di, ep [Diet Therapy, Prevention & Control, Etiology, Diagnosis, Epidemiology]
223. ("cancer risk" or "melanoma risk" or "lymphoma risk" or "leukemia risk" or "myeloma risk" or "sarcoma risk").tw.
224. (("risk of" or "occurrence of") and (cancer$ or neoplasm$ or malignan$ or adenocarcinom$ or carcinom$ or melanom$ or lymphom$ or leuk?emi$ or myelodysplas$ or myelom$ or sarcom$)).tw.
225. 222 or 224 or 223
226. colon polyps.mp. or exp adenomatous polyps/ or exp colonic polyps/
227. (colon$ or rectum or rectal or colorectum or colorectal).ti,ab.
228. (adenoma$ or polyps or polyp).ti,ab.
229. 228 and 227
230. 229 or 226
231. mammography.mp. or exp mammography/
232. mammog$.ti,ab.
233. 231 or 232
234. dens$.ti,ab.
235. 233 and 234
236. prostate specific antigen.mp. or exp prostate-specific antigen/
237. (aberrant crypt$ foc$ or ACF).ti,ab.
238. (prostat$ and (intraepitheli$ or intra-epitheli$ or intra epitheli$) and Neoplas$).ab,ti.
239. 236 or 238 or 235 or 237 or 230
240. type 1 diabetes mellitus.mp. or exp Diabetes Mellitus, Type 1/
241. psoriasis.mp. or exp Psoriasis/
242. rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/
243. multiple sclerosis.mp. or exp Multiple Sclerosis/
244. inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
245. ulcerative colitis.mp. or exp Colitis, Ulcerative/

246. Crohn's disease.mp. or exp Crohn Disease/
247. 240 or 241 or 242 or 243 or 244 or 245 or 246
248. tuberculosis.mp. or exp Tuberculosis/
249. influenza.mp. or exp Influenza, Human/
250. 248 or 249
251. exp "Activities of Daily Living"/
252. muscle strength.mp. or exp Muscle Strength/
253. exp Musculoskeletal Equilibrium/ or exp Walking/
254. ("balance test" or "timed walk" or "physical performance" or "hand-grip strength").tw.
255. exp Hand Strength/
256. exp Muscles/
257. ("walking time" or "muscle strength").tw.
258. or/251-257
259. limit 258 to ("all adult (19 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
260. exp Pre-eclampsia/
261. (pre-eclampsia or preeclampsia).mp.
262. pregnancy complication$.mp. or exp Pregnancy Complications/
263. or/260-262
264. limit 263 to male
265. limit 263 to female
266. 264 not 265
267. 263 not 266
268. limit 267 to animal
269. limit 267 to human
270. 268 not 269
271. 267 not 270
272. limit 271 to english language
273. exp infant,low birth weight/
274. low birth weight.af.
275. exp infant, premature/
276. ("small for gestational age" or sga).af.
277. ((preterm or prematur$) adj6 (infant or newborn)).af.
278. or/273-277
279. exp Milk, Human/
280. human milk.mp.
281. (human adj2 milk).tw.
282. breast milk.mp.
283. breastmilk.mp.

284. breast feeding.mp.
285. breastfeed$.mp.
286. breast fed.mp.
287. breastfed.mp.
288. (breast adj2 fed).tw.
289. exp lactation/
290. (lactating or lactation).mp.
291. or/279-290
292. Mortality.mp. or exp Mortality/
293. Fatal Outcome.mp. or exp Fatal Outcome/
294. exp Death/ or exp "Cause of Death"/ or death.mp.
295. Survival Rate.mp. or exp Survival Rate/
296. 295 or 292 or 294 or 293
297. heterotopic ossification.mp. or exp Ossification, Heterotopic/
298. myositis ossificans.mp. or exp Myositis Ossificans/
299. calcinosis.mp. or exp Calcinosis/
300. extraosseous calcification.mp.
301. metaplastic calcification.mp.
302. myo-osteosis.mp.
303. neurogenic osteoma.mp.
304. osseous heteroplasia.mp.
305. ossifying fibromyopathy.mp.
306. para-articular calcification.mp.
307. heterotopic calcification.mp.
308. pathological bone.mp.
309. pathological calcification.mp.
310. periarticular calcification.mp.
311. synostosis.mp.
312. ectopic bone.mp.
313. heterotopic bone.mp.
314. dystrophic ossification.mp.
315. ectopic ossification.mp.
316. metaplastic ossification.mp.
317. para-articular ossification.mp.
318. periarticular ossification.mp.
319. pathological ossification.mp.
320. ectopic calcification.mp.
321. soft tissue calcification.mp.

322. (vascular adj3 calcification).mp.
323. (aort$ adj3 calcification).mp.
324. (valv$ adj3 calcification).mp.
325. or/297-324
326. limit 325 to animal
327. limit 325 to human
328. 326 not 327
329. 325 not 328
330. limit 329 to english language
331. exp kidney disease/
332. exp kidney/
333. kidney.mp.
334. renal.af.
335. nephro$.af.
336. exp renal replacement therapy/
337. exp kidney, artificial/
338. (hemodialy$ or haemodialy$ or dialy$).af.
339. exp Kidney Glomerulus/
340. exp Kidney Function Tests/
341. ur?emia.tw.
342. exp Kidney Calculi/
343. (kidney stone$ or renal stone$ or renal calcul$ or kidney calcul$ or nephrolith$).af.
344. 343 not 342
345. exp nephrolithiasis/
346. or/331-345
347. allerg$.mp. or exp Hypersensitivity/

b. Overall Search Strategy for Outcomes of Upper Limits

Database: Ovid MEDLINE(R), CCTR (from 1966 to December 2008)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
4. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/

9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol$.tw.
12. Cholecalciferol/
13. Cholecalciferol$.tw.
14. calciferol.tw.
15. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
16. or/1-15
17. supplement$.tw.
18. exp Dietary Supplements/to, ae, po, ut [Toxicity, Adverse Effects, Poisoning, Utilization]
19. No-Observed-Adverse-Effect Level/
20. upper limit$.tw.
21. UL.tw.
22. (excess$ or toxic$).tw.
23. vit d intox$.tw.
24. (noael or noel).tw.
25. (no observed adj2 effect$).tw.
26. or/17-25
27. 26 and 16
28. (ANIMALS not HUMAN).sh.
29. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
30. 27 not 28
31. 30 not 29
32. limit 31 to (addresses or bibliography or biography or comment or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or "review")
33. 31 not 32
34. limit 33 to english language
35. exp kidney disease/
36. exp kidney, artificial/
37. exp Kidney Function Tests/
38. ur?emia.tw.
39. (kidney stone$ or renal stone$ or renal calcul$ or kidney calcul$ or nephrolith$).af.
40. exp nephrolithiasis/
41. heterotopic ossification.mp. or exp Ossification, Heterotopic/
42. myositis ossificans.mp. or exp Myositis Ossificans/
43. calcinosis.mp. or exp Calcinosis/
44. extraosseous calcification.mp.
45. metaplastic calcification.mp.

46. myo-osteosis.mp.
47. neurogenic osteoma.mp.
48. osseous heteroplasia.mp.
49. ossifying fibromyopathy.mp.
50. para-articular calcification.mp.
51. heterotopic calcification.mp.
52. pathological bone.mp.
53. pathological calcification.mp.
54. periarticular calcification.mp.
55. synostosis.mp.
56. ectopic bone.mp.
57. heterotopic bone.mp.
58. dystrophic ossification.mp.
59. ectopic ossification.mp.
60. metaplastic ossification.mp.
61. para-articular ossification.mp.
62. periarticular ossification.mp.
63. pathological ossification.mp.
64. ectopic calcification.mp.
65. soft tissue calcification.mp.
66. (vascular adj3 calcification).mp.
67. (aort$ adj3 calcification).mp.
68. (valv$ adj3 calcification).mp.
69. or/41-68
70. Calcification, Physiologic/de [Drug Effects]
71. Hypercalcemia/
72. Kidney Calculi/
73. Nephrocalcinosis/
74. Urinary Calculi/
75. Bladder Calculi/
76. Ureteral Calculi/
77. Calcinosis/
78. Hypercalcemi$.tw.
79. (Burnett$ adj2 syndrome$).tw.
80. Hypercalciuri$.tw.
81. or/70-80
82. psoriasis.mp. or exp Psoriasis/
83. 81 or 69 or 82

84. 34 and 83
85. limit 84 to case reports
86. 84 not 85

Appendix B. Search strategy for systematic reviews

Databases: MEDLINE(R), the Cochrane Database of Systemic Reviews, and the Health Technology Assessments (up to December 2008)

1. (meta-analys$ or metaanalys$).mp. [mp=title, abstract, full text, keywords, caption text]
2. (systematic review$ or systematic literature or evidence-based or evidence review$).mp. [mp=title, abstract, full text, keywords, caption text]
3. (EBM or EBR or EBRs).mp. [mp=title, abstract, full text, keywords, caption text]
4. or/1-3
5. (vitamin D or cholecalciferol or ergocalciferol or hydroxy vitamin D or calcitriol).mp. [mp=title, abstract, full text, keywords, caption text]
6. Calcium.mp. [mp=title, abstract, full text, keywords, caption text]
7. 5 or 6
8. 4 and 7

Appendix D. Evaluation of existing systematic reviews and evidence tables of the qualified systematic reviews

Evaluation of existing systematic reviews

Author Year Journal /Source	Intervention or exposure	Outcome	Study design included	Healthy population at baseline?*	Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?***	Clear reporting of comparison and control group?	Clear reporting of outcome definitions?	Clear reporting of study designs (need separate reporting if two or more different designs are included)?	Comments* ** ***
Autier 2007 Arch Intern Med [17846391][1]	Vitamin D [+/- Calcium]	All cause mortality	RCTs	Yes[1]	Yes	Yes	Yes	Yes	One additional study found
Avenell 2008 Cochrane Database of Systematic Reviews [16034849][2]	Vitamin D [+/- Calcium]	All cause mortality	RCTs	Yes	Yes	Yes	Yes	Yes	All relevant studies included in Autier 2007 – Conclusions are same as Autier 2007.
Allender 1996 Ann Intern Med	Ca supplement	Blood pressure	RCT	Yes (subgroup analysis)	Yes	Yes	Yes	Yes	26 of 64 potential RCTs
Cappuccio 1995 AJE	Ca intake	Blood pressure	Observational, including cross-sectional	Unclear	No	NA (regressions)	Yes	No	REJECT Includes XS
Dickinson 2008 Cochrane	Ca supplement	Blood pressure	RCT	No All with HTN	Yes	Yes	Yes	Yes	Revision of 2006 SR 15/64 potential RCTs

[1] We excluded a study on patients with congestive heart failure in our reanalysis of data from this systematic review

Author Year Journal /Source	Intervention or exposure	Outcome	Study design included	Healthy population at baseline?*	Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?***	Clear reporting of comparison and control group?	Clear reporting of outcome definitions?	Clear reporting of study designs (need separate reporting if two or more different designs are included)?	Comments****
Griffith 1999 AJH	Ca supplement	Blood pressure	RCT	Yes & No HTN & NTN combined See comment	Yes	Yes	Yes	Yes	Update of Bucher 1996 [2263] Subgp analysis HTN vs NTN in Bucher only 42/64 potential RCTs
van Mierlo 2006 J Hum Hypert	Ca supplement	Blood pressure	RCT	Yes Subgroup of HTN & NTN	Yes	Yes	Yes	Yes	40/64 potential RCTs
Trumbo 2007 Nutr Rev	Ca supplement	Blood pressure, HTN, Pregnancy-induced HTN	All	Yes Subgroup of HTN & NTN	Yes (interv) No (observ)	No	No	No	REJECT Qualitative only Count of sig studies only Unclear if SR.
Bergsma-Kadijk 1996 Epidemiology	Ca intake	cancer and polyp	Cohort and Case-control	nd (probably healthy population)	nd on dietary assessment method	nd on Ca intake (only RR/OR between lowest and highest categories reported)	nd	nd on the definition of case-control study	Reject
Weigarten 2008 Cochrane Database of Systematic Reviews	Ca supplement (>1200 mg/d)	cancer and polyp	RCT	yes (pts with prior adenoma)	yes	yes	yes	yes	Accept

Author Year Journal /Source	Intervention or exposure	Outcome	Study design included	Healthy population at baseline?*	Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?***	Clear reporting of comparison and control group?	Clear reporting of outcome definitions?	Clear reporting of study designs (need separate reporting if two or more different designs are included)?	Comments***
Davies 2006 J Natl Cancer Inst	Nutritional RCTs, including Ca supplement	Cancer, recurrence of preinvasive lesions	RCT	No (both pts with cancer and preinvasive lesions)	nd	no	no	yes	Part of a larger SR of both diet and physical activity on outcome among patients with cancer or preinvasive lesions
Bergel 2007 BMC Pediatrics	maternal calcium intake	offspring BP	RCTs & cohort	y (RCT)	no yes	yes	yes	no	Data from 2 RCTs may be useful. Reject
Carroli 1994 Brit J Obstet Gynecol	Ca supplement	Preeclampsia	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Hofmeyer 2003 S African J	Ca Supplement	Preeclampsia	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Hofmeyer 2007 S African J	Ca Supplement	Preeclampsia (and summary of the outcomes mentioned above)	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR

Author Year Journal /Source	Intervention or exposure	Outcome	Study design included	Healthy population at baseline?*	Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?***	Clear reporting of comparison and control group?	Clear reporting of outcome definitions?	Clear reporting of study designs (need separate reporting if two or more different designs are included)?	Comments* ** ***
Hoffmeyr 2006 Cochrane Database of Systematic Reviews	Ca supplement	Preeclampsia, pregnancy induced hypertension with and without proteinuria, maternal death or serious morbidity, other maternal outcomes, stillbirth, neonatal mortality or morbidity, preterm birth, small gestational age, and other outcomes for the child	RCT	Yes	Yes	Yes	Yes	Yes	Eligible review
Bucher 1996 JAMA	Ca supplement	Preeclampsia, pregnancy-induced hypertension	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Gao 2005 NCI	calcium intake or dairy product	prostate cancer	prospective cohort	yes (assumed from study design)	yes	yes	yes	yes	
Shaukat 2005 Am J Gastroenterol	Ca supplement	recurrent polyp	RCT	yes (pts with prior adenoma)	no (1/3 included Ca+Vit A/C/E+selenium)	yes	yes? "recurrence of adenoma"	yes? "RCT"	Reject

Author Year Journal /Source	Intervention or exposure	Outcome	Study design included	Healthy population at baseline?*	Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?***	Clear reporting of comparison and control group?	Clear reporting of outcome definitions?	Clear reporting of study designs (need separate reporting if two or more different designs are included)?	Comments****
Barr 2003 J Nutr	Increased dairy product or calcium intake (from supplements)	Weight	RCTs	Yes "healthy"	Yes (separate studies of increased dairy product and those of calcium supplements)	yes	yes	yes	No meta-analysis. Included children and adults
Trowman 2006 Br J Nutr	Calcium supplements or increased provision of dairy products	Weight	RCTs	Yes (excluded populations with severe co-morbidities, such as renal problems or cancer)	Yes (Separate meta-analyses for calcium supplement and increased provision of dairy products)	yes	yes	yes	May need to redo the meta-analyses to separate out energy restriction diet studies. This SR included adults only.
Winzenberg 2007 Obesity	calcium supplementation food or chemical	weight	RCTs	yes	yes	yes	yes	yes	2º analysis of RCT of calcium on bone density outcome
Lanou 2008 Nutr Rev	Calcium or dairy supplementation with or without energy restriction	Weight, body fat	RCTs	nd	yes	no	yes	yes	Included both dairy and calcium supplementation RCTs. No individual study characteristics reported

*Either included only healthy population at baseline or SR had separate analyses for population with diseases and without diseases
**For SR of interventional studies
***For SR of observational studies
****Please comment on issues such as update of previous SRs or specific reasons for using or not using the SR, other than not fulfilling the screening criteria.

Evidence table of systematic review of the effect of vitamin D on bone health

Author Year [PMID]	Cranney 2007 [18088161]
Design	Systematic review of RCTs and observational studies
Population	• Include all ages • Exclude secondary causes of osteoporosis (e.g., glucocorticoid-induced, renal or liver disease) • Exclude studies on the treatment of vitamin D-dependent rickets (to minimize clinical heterogeneity as treatments is often non-dietary sources of vitamin D)
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include vitamin D_2 or D_3 with or without calcium. • Exclude vitamin D preparations, calcitriol, alphacalcidol (because they are not nutritional supplements, and have different safety profile) Comparator: • No vitamin D or lower doses/levels of vitamin D
Results	See text for summary results for the following outcomes in both vitamin D and combined vitamin D and calcium sections of the report: • Rickets • Fractures, falls, or performance measures • Bone mineral density or bone mineral contents • How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D Concentrations • Adverse events
Comments	Case-control studies were included but always summarized separately from cohort studies and RCTs. Meta-analyses were performed to pool results from RCTs only.

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Evidence table of systematic review on vitamin D supplementation and all-cause mortality

Author Year [PMID]	Autier 2007 [17846391]
Design (Search Years)	Randomized controlled trials (1992-2006)
Population	Community dwelling or institutionalized adults
Intervention (Exposure) and Comparator	Supplementary vitamin D (at least 1000 mg/d) without calcium vs. placebo or no treatment
Results	18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (± calcium) supplementation Statistically homogeneous In our reanalysis we and excluded 3 of 18 trials and separated studies with vitamin D only from those with vitamin D and calcium combination. For details and results of our reanalysis, see text.
Comments	See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail.

AMSTAR Criteria

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	No	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores)	

Evidence table of systematic review of calcium on growth in children

Author Year [PMID]	Winzenberg 2007 [17636098]
Design (Search Years)	Randomized controlled trials (1966-2005)
Population	Children <18 y
Intervention (Exposure) and Comparator	Supplemental and dietary calcium 300-1200 mg/d vs. placebo
Results	17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) Kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity

Comments	Post hoc analysis performed on trials identified for a metaanalysis of randomized controlled trials of calcium on bone outcomes

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Unclear if all languages included; study quality assessed but not factored into the M-A	

Evidence table of systematic review s of calcium and blood pressure

Author Year [PMID]	Griffith 1999 [10075392]
Design (Search Years)	Randomized controlled trials (1966-1997)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 600-2000 mg (36% 1000 mg; 26% 1500-1600 mg; 12% 2000 mg)
Results	42 trials SBP: -1.44 (-2.20, -0.68)[2]; statistically heterogeneous DBP: -0.84 (-1.44, -0.24); statistically heterogeneous Subgroup analyses did not find that heterogeneity could be explained by age, sex, baseline calcium, dietary versus nondietary calcium, or quality. Subgroups with hypertensive versus normotensive people were significantly different (no further details). Conclusions similar to previous systematic review (Bucher 1996{2263 /id})
Comments	Update of Bucher 1996{2263 /id} (see below).

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Study quality not discussed in conclusions. Funding source reported, but not conflict of interest.	

Author Year [PMID]	van Mierlo 2006 [16673011]
Design (Search Years)	Randomized controlled trials (1966-2003)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Calcium supplementation versus placebo (no supplement) Dose range 355-2000 mg (40% 1000 mg; 32% 1500-1600 mg; 6% 2000 mg)
Results	40 trials SBP: -1.86 (95% CI -2.91, -0.81); statistically heterogeneous DBP: -0.99 (95% CI -1.61, -0.37); statistically heterogeneous In multivariable analysis including age, sex, initial calcium intake, calcium dose, and initial blood pressure:

		SBP	DBP
Age	<45 y	-1.45 (-2.99, +0.09)	-1.26 (-2.20, -0.33)
	≥45 y	-2.33 (-3.69, -0.96)	-0.80 (-1.62, +0.02)
Male	≤50%	-2.20 (-3.68, -0.72)	-1.12 (-1.98, -0.26)
	>50%	-1.77 (-3.13, -0.42)	-0.84 (-1.65, -0.04)
Initial BP	<140/90 mm Hg	-2.04 (-3.40, -0.68)	-1.04 (-1.86, -0.22)
	≥140/90 mm Hg	-1.85 (-3.45, -0.32)	-0.89 (-1.79, +0.01)
Ca dose	≤1000 mg	-2.17 (-3.59, -0.75)	-1.41 (-2.24, -0.59)
	>1000 mg	-1.75 (-3.20, -0.31)	-0.56 (-1.40, +0.29)

Blood pressures not statistically significantly different between any strata.

Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Unclear	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Partial	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	No data on inclusion of unpublished data. Excluded studies available from authors	

[2] Numbers in parentheses are 95% confidence intervals

Evidence table of systematic review s of calcium and blood pressure. continued

Author Year [PMID]	Bucher 1996 [8596234]
Design (Search Years)	Randomized controlled trials (1966-1994)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 406-2000 mg (41% 1000 mg; 31% 1500-1600 mg; 8% 2000 mg)
Results	33 trials [Overall summary results were updated in Griffith 1999{1927 /id}, above] Studies with specified subgroups of hypertensive and normotensive participants (6 trials): Hypertensives SBP -4.30 (-6.47, -2.13) DBP -1.50 (-2.77, -0.23) Normotensives SBP -0.27 (-1.80, +1.27) DBP -0.33 (-1.56, +0.90) Regression analyses: BP (continuous scale) SBP OR = 0.99 (0.96, 1.01) DBP OR = 0.99 (0.96, 1.03) Dose of calcium, duration of supplementation, dietary vs nondietary calcium supplementation, methodological quality did not demonstrate a relationship with the magnitude of treatment effect.
Comments	Updated in Griffith 1999{1927 /id} (see above)

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Funding source reported, but not conflict of interest.	

Author Year [PMID]	Allender 1996 [8610952]
Design (Search Years)	Randomized controlled trials (1982-1993)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2160 mg (35% 1000 mg; 29% 1500-1600 mg; 10% 2000 mg)
Results	26 trials (22 trials included in metaanalyses) SBP: -0.89 (-1.74, -0.05) DBP: -0.18 (-0.75, +0.40) Hypertensives SBP -1.68 (-3.18, -0.18) DBP +0.02 (-0.96, +1.00) Normotensives SBP -0.53 (-1.56, +0.49) DBP -0.28 (-0.99, +0.42) By weighted linear regression analyses, age, sex, calcium dose, trial duration were not associated with treatment effect (P>0.10)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Author Year [PMID]	Cappuccio 1989 [2697729]
Design (Search Years)	Randomized controlled trials (1983-1988)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Nondietary calcium supplementation versus placebo (no supplement) or low calcium intake Dose range 800-1600 mg (60% 1000 mg; 27% 1500-1600 mg)
Results	15 trials SBP (supine): -0.13 (-0.46, +0.19) DBP (supine): +0.03 (-0.17, +0.22) Hypertensives SBP +0.06 (-0.59, +0.72) DBP +0.03 (-0.21, +0.27)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	nd	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Evidence table of systematic review s of calcium and blood pressure. continued

Author Year [PMID]	Dickinson 2006 [16625609][3]
Design (Search Years)	Randomized controlled trials (1982-2003/2005[4])
Population	Hypertensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2000 mg (50% 1000 mg; 25% 1500-1600 mg; 6% 2000 mg)
Results	13 trials SBP: -2.53 (-4.45, -0.60); statistically heterogeneous DBP: -0.81 (-2.07, +0.44); statistically heterogeneous Ca dose <1200 mg SBP -2.67 (-5.15, -0.18) DBP -0.75 (-2.13, +0.63) Ca dose 1200-2000 mg SBP -2.69 (-5.86, +0.47) DBP -0.78 (-3.82, +2.25) Not statistically significantly different by calcium dose
Comments	

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Evidence table of systematic review of calcium on growth in children

Author Year [PMID]	Winzenberg 2007 [17636098]
Design (Search Years)	Randomized controlled trials (1966-2005)
Population	Children <18 y
Intervention (Exposure) and Comparator	Supplemental and dietary calcium 300-1200 mg/d vs. placebo
Results	17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) Kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity
Comments	Post hoc analysis performed on trials identified for a metaanalysis of randomized controlled trials of calcium on bone outcomes

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Unclear if all languages included; study quality assessed but not factored into the M-A	

[3] A technical update, with no further studies added was published in the Cochrane database in 2008.
[4] Different dates for different databases.

Evidence table of systematic review on calcium intake and adenoma recurrence

Author Year [UI]	Weingarten, 2008 [18254022]
Design	Randomized controlled trials: Cochrane Library Issue 2, 2007, the Cochrane Colorectal Cancer Group (CCCG) specialized register, MEDLINE (1966 to July 2007), Cancerlit (1963 to April 2002), Embase (1980 to July 2007)
Population	Healthy adults and studies of adults at higher risk of colon cancer due to family history, previous adenomatous polyps, or inflammatory bowel disease
Intervention (Exposure) and Comparator	Calcium (>1200 mg/d) vs. placebo
Results	Calcium vs. placebo colorectal adenoma recurrence: OR 0.74, CI 0.58-0.95, P=0.02 CRC: OR 0.34, CI 0.05-2.15, P=0.20 at least one adverse event requiring discontinuation: OR 0.93, CI 0.42-2.05, P=0.80
Comments	Based only on two RCTs (1346 participants). Heterogeneity due to different dose of supplementation (one RCT supplemented with 1200 mg/d and the other RCT with 2000 mg/d). Analysis based on fixed effects model; however, considering there are only two studies, random effects model might have been more appropriate. Analysis on adverse events is based only on reported data of one out of the two RCTs (Barron 1999). Only participants with high risk due to previous adenomas were recruited in these two RCTs; therefore, applicability of the results can only be considered for high risk population. Insufficient evidence to recommend the general use of calcium supplements to prevent colorectal adenoma or colorectal cancer

AMSTAR

A priori design?	X	**Study quality assessment performed?**	X
Two independent reviewers?	X	**Study quality appropriately used in analysis?**	X
Comprehensive literature search?	X	**Appropriate statistical synthesis?**	X
All publication types and languages included?		**Publication bias assessed?**	
Included and excluded studies listed?	X	**Conflicts of interest stated?**	X
Study characteristics provided?	X		

Appendix E. Blank Data Extraction Form and Quality Assessment Checklists

ELIGIBILITY CRITERIA AND OTHER CHARACTERISTICS

UI	Author Year	Study Design*	Inclusion	Exclusion	Enrollment Years	Trial or Cohort Name	Funding Source	Extractor
		RCT RCT-post hoc** Other intervention study Cohort study Case-cohort study						

*Leave appropriate choice of study design and delete all others
**Post hoc analyses of an existing RCT for outcomes that were not planned in the original RCT

POPULATION (BASELINE)**

UI	Author Year	Study Design*	Location (e.g., City and Country, latitude)	N enrolled***	N analyzed	Mean (SD) Age, yr	Age Range / IQR	Male, %	Race / Ethnicity	Anthropometry data (e.g., BMI, weight, or %body fat …etc)	Health Status	Specific Nutrition Status Data (e.g., malnourish, low Vit D or Ca intake …etc.)

*Please copy from above
**Report baseline data for all subjects: preferred data for subjects actually analyzed than for subjects that enrolled in the study.
***For RCT, N enrolled is the number of subjects randomized. For cohort study, N enrolled is the total number of subjects fulfilled study inclusion criteria. For case-cohort study, please report as detailed information as possible on subjects selection. For example, original cohort sample size, number of subjects provided exposure data (eg. blood sample or dietary assessment), number of subjects had outcome data …etc.

Background Diet*

UI	Author Year	Exposure	Dietary Assessment Method**	Food Composition Database***	Internal Calibration (or Validity) of Dietary Assessment? (y/n) If Yes, Provide Data	Biomarker Assay****	Analytical Validity of Biomarker Data Reported? (y/n) If Yes, Provide Data	Time between Biomarker Sampling and Analysis	Season/Date when the biomarker samples were drawn	Background exposure data
		25(OH)D and/or $1,25(OH)_2D$								
		Dietary calcium intake								

* Write “nd” if there was no data reported. Please do not leave blank
**Please refer to common dietary assessment method table. If other method was used, please describe the detail. Otherwise, please simply use the brief name described in the table
***USDA Nutrient Database, Minnesota Food and Nutrient Database (NDSR), Food product manufacturer, McCance and Widdowson's food table, Country-specific food tables, Other nutrient analysis (please specify)
****ONLY biomarker of interest for calcium is calcium balance

INTERVENTION(S), SKIP IF OBSERVATIONAL STUDY

UI	Author Year	Intervention(s)	Source (e.g., brand name, foods, or formulation)	Vit D and/or Ca Total Daily Dose	Intervention Duration	Intervention Frequency (e.g. capsules were taken 2 times a day)
Co-intervention(s) *:						
Compliance/Adherence:						

Duplicate one row per intervention, including control intervention.
*Report the non-vit D or Ca intervention(s) (e.g., other drug intervention, or background low-fat diet). We are interested in only independent effect of vitamin D and/or calcium. Therefore, describe how effects of co-intervention(s) were controlled for in the analyses or study design.

LIST OF ALL OUTCOMES

UI	Author Year	Primary / Secondary Outcome**	Outcome	Definition

Duplicate one row per outcome of interest. Only need to list outcomes that were included in the result section.
**Must have been explicitly stated in the original paper. Otherwise, please enter "nd"

UI	Author Year	Comments

-----Confounders: Please report all confounders controlled in the analyses reported in the following result section (adjusted results)

UI	Author Year	Confounder Groups	Please List Name of Confounder (including matching factors)	Specific comments for confounders
		Other nutrients or dietary factors (e.g., certain food consumption), including supplement use and total energy intake		
		Demographics (e.g., age, gender, race, education)?	Yes/no*	
		Anthropometrics (e.g., BMI, body weight, % body fat)?	Yes/no*	
		Medical conditions		
		Medication		
		Sunlight exposure and its proxy variables (e.g., seasonal variation of 25(OH)D, UV exposure, location)		
		Smoking and other life styles variables (e.g., physical activity, occupation, alcohol consumption)	Yes/no*	
		Other		

*Please choose "yes" if any one of the confounders in this group was controlled in the analysis

FOLLOWING IS RESULT SECTION. PLEASE CHOOSE APPROPRIATE TYPE OF DATA COLLECTION TABLE FOR ALL OUTCOMES OF INTEREST

-----Main Analyses (For analyses that adjusted for confounders, choose the "best" model)

2 ARMS/GROUPS: DICHOTOMOUS OUTCOMES (e.g. OR, RR, %death)

UI	Author Year	Outcome	Exposure / Intervention	Mean Follow-up, mo	N Event	N Total	Outcome Metric (e.g. OR, RR, HR, %) and direction of comparison*	Unadjusted			Adjusted		
								Result	95% CI	P btw	Result	95% CI	P btw

*Example: OR Ca/placebo

2 ARMS/GROUPS: CONTINOUS OUTCOMES (e.g. BMD, BP)

UI	Author Year	Outcome	Unit	Exposure / Intervention	Mean Follow-up, mo	No. Analyzed	Baseline	Baseline CI / SE / SD*	Final or Delta**	Final or Delta CI / SE / SD*	Net difference	Net difference CI / SE / SD*	P between

Baseline=baseline value; Final=final value; Delta=change value from baseline, which is Final-Baseline value; Net difference=differences in deltas
*Enter outcome metric reported in the unadjusted or adjusted result section
**Delta value is preferred than the Final value. Please report the direction for the change by using "+" or "-" sign: e.g. +2.8 or -2.8

≥2 ARMS/GROUPS: DICHOTOMOUS OUTCOMES (e.g. OR, RR, %death)

UI	Author Year	Outcome	Exposure Categories(e.g., Tertiles) / Intervention Groups	Mean Vit D level / dose	Mean Ca level / dose	No. of Cases (Event)*	No. of Non-cases / Total N**	Mean Follow-up, mo	Crude or Adjusted analysis?	Outcome Metric (e.g. OR, RR, HR, %)	Outcome effect size	CI / SE / SD **	P between groups***	P for trend****

Duplicate one row per exposure category or intervention group.
*Number of subjects with outcome
**Please choose one and delete the others
***Specify the comparison. For example group 1 vs. 3 = -6; group 1 vs. 2 = -8
****P value for testing the linear trend of the OR/RR across different categories or doses

≥2 ARMS/GROUPS: CONTINOUS OUTCOMES (e.g. BMD, BP)

UI	Author Year	Outcome	Unit	Exposure Category / Intervention Group	Crude or Adjusted analysis?	Mean Follow-up (months)	No. Analyzed	Baseline	Baseline CI / SE / SD*	Final or Delta**	Final or Delta CI / SE / SD*	Net difference***	Net difference CI / SE / SD*	P between groups***

Duplicate one row per exposure category or intervention group. Please write "nd" if there was no data reported. DO NOT LEAVE BLANK.
*Please choose one and delete the others
**Delta value is preferred than the Final value. Please report the direction for the change by using "+" or "-" sign: e.g. +2.8 or -2.8
***Specify the comparison. For example group 1 vs. 3 = -6; group 1 vs. 2 = -8

MEAN DATA. THIS SHOULD ONLY APPLY TO CASE-COHORT STUDIES THAT COMPARE BASELINE VIT D / CA LEVELS BETWEEN CASES (WITH DISEASE) AND CONTROLS (WITHOUT DISEASE)

UI	Author Year	Outcome Group	Time between Baseline Exposure and Outcome Assessments	Crude or Adjusted analysis?	No. Analyzed	Mean 25(OH)D Level	Vit D level CI / SE / SD*	Mean Ca intake or Ca balance	Ca CI / SE / SD*	P between groups
		Cases:								
		Control:								

Duplicate one table per outcome

OTHER RESULTS. ONLY USE THE FOLLOWING BOX WHEN THE TYPE OF RESULT DATA DO NOT FIT THE TABLES PROVIDED ABOVE

UI	Author Year	Outcome	Results

UI	Author Year	Comments for Results

-----Subgroup Analyses

Please copy the appropriate table above for all subgroup analyses of interest.

QUALITY of INTERVENTIONAL STUDIES

UI	Author Year	Design*	Appropriate Randomization Technique (y/n/nd/NA)	Allocation Concealment (y/n/nd/NA)	Appropriate Washout Period (y/n/nd/NA)	Dropout Rate <20%	Blinded Outcome Assessment (y/n/nd)	Intention to Treat Analysis (y/n/nd)	Appropriate Statistical Analysis** (y/n)	Assessment for Confounding (y/n/nd/NA)	Clear Reporting with No Discrepancies (y/n)	OVERALL Grade

Adverse Event(s): **	
Explanation for Overall Quality Grade (if not Grade A):	

NA=not applicable

***Please do not copy the 4 categories of study designs from above sections. Specify the exact study design: RCT – Parallel, RCT – Cross-over, RCT – Cluster, quasi-RCT, Non-randomized, but controlled trial, before-and-after trial, other interventional design (please explain in detail)**

****Please do not leave blank. Type nd if there was no data on adverse events.**

QUALITY of COHORT OR NESTED CASE-CONTROL STUDIES

UI	Author Year	Population	Exposure (All)	Dietary assessment*	Biomarkers*	Comparator	Statistical Analysis	Outcome	Design
		a) Eligibility criteria clear? (y/n)	a) Exposure assessor blinded to outcome info? (y/n)	a) Method reported? (y/n)	a) One of the prespecified methods*** was used? (y/n)	a) Level of the exposure in comparative categories (eg quartiles) is given (ranges)? (y/n) applicable for categorical analyses only	a) Adjusted or matched for ANY confounders (other than age and sex)?** (y/n)	a) Clear definition of outcome, including time of ascertainment? (y/n)	a) Prospective collection of data? (y/n)
		b) Sampling of population random or consecutive? (y/n)	b) Outcome assessor blinded to exposure measurement? (y/n)	b) Food composition database or suppl composition reported? (y/n)	Time from sample collection to sample analysis reported? (y/n)			b) Loss to follow-up <20%? (y/n)	b) Analysis was planned when cohort was formed? (y/n)
				c) Internal calibration of method perform (if FFQ)? (y/n/NA)			b) Justification of final adjusted model selection? (y/n)	c) Do the authors specify a primary outcome? (y/n)	c) Justification of sample size (includes sample size calculations)? (y/n)

OVERALL Grade (A/B/C):	
Explanation for Overall Quality Grade (if not Grade A):	

***Check "NA" and skip all questions if study did not use dietary assessment or biomarkers**

****We will judge in the end if the set of confounders is adequate**

*****Prespecified methods: HPLC, RIA kits, LC-MS/MS; EIA/Chemiluminescence**

Appendix F. Excluded Studies

Excluded Study	Reason
Aalberts JS, Weegels PL, van der HL et al. Calcium supplementation: effect on blood pressure and urinary mineral excretion in normotensive male lactoovovegetarians and omnivores. American Journal of Clinical Nutrition 48 (1):131-8, 1988.	No outcomes of interest
Abbasi AA, Chemplavil JK, Farah S, Muller BF, Arnstein AR. Hypercalcemia in active pulmonary tuberculosis. Annals of Internal Medicine 90 (3):324-8, 1979.	No UL outcomes
Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. Journal of Pediatrics 2007; 151(3):293-298.	Not a calcium intervention trial
Adams JS, Lee G. Gains in bone mineral density with resolution of Vitamin D intoxication. Annals of Internal Medicine 127 (3):203-6, 1997.	Case report
Akcakus M, Koklu E, Budak N, Kula M, Kurtoglu S, Koklu S. The relationship between birthweight, 25-hydroxyVitamin D concentrations and bone mineral status in neonates. Annals of Tropical Paediatrics 2006; 26(4):267-275.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant Vitamin D supplementation. Archives of Disease in Childhood 61 (12):1159-63, 1986.	Not RCT arrow 4 study
Ala-Houhala M. 25-HydroxyVitamin D levels during breast-feeding with or without maternal or infantile supplementation of Vitamin D. Journal of Pediatric Gastroenterology & Nutrition 4(2):220-6, 1985.	In Ottawa EPC report
Almendingen K, Hofstad B, Vatn MH. Dietary habits and growth and recurrence of colorectal adenomas: results from a three-year endoscopic follow-up study. Nutrition & Cancer 49 (2):131-8, 2004.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Almendingen K, Hofstad B, Vatn MH. Lifestyle-related factors and colorectal polyps: preliminary results from a Norwegian follow-up and intervention study. European Journal of Cancer Prevention 11(2):153-8, 2002.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Almendingen K, Trygg K, Hofstad B, Veierod MB, Vatn MH. Results from two repeated 5 day dietary records with a 1 y interval among patients with colorectal polyps. European Journal of Clinical Nutrition 55 (5):374-9, 2001.	No outcomes of interest
Al-oanzi ZH, Tuck SP, Raj N et al. Assessment of Vitamin D status in male osteoporosis. Clinical Chemistry 52 (2):248-54, 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK. Optimal Vitamin D status and serum parathyroid hormone concentrations in African American women. American Journal of Clinical Nutrition 84 (3):602-9, 2006.	No outcomes of interest
Anonymous. Calcium supplementation during pregnancy reduces the risk of developing preeclampsia in nulliparous women. Canadian Family Physician 45:614, 618-20, 1999.	Editorial-like brief review

Excluded Study	Reason
Anonymous. Vitamin D supplementation for northern native communities. Indian and Inuit Health Committee, Canadian Paediatric Society. CMAJ Canadian Medical Association Journal 138 (3):229-30, 1988.	Review paper
Armitage NC, Rooney PS, Gifford KA, Clarke PA, Hardcastle JD. The effect of calcium supplements on rectal mucosal proliferation. British Journal of Cancer 71 (1):186-90, 1995.	No outcomes of interest
Armstrong AL, Oborne J, Coupland CA, Macpherson MB, Bassey EJ, Wallace WA. Effects of hormone replacement therapy on muscle performance and balance in post-menopausal women. Clinical Science 91 (6):685 -90, 1996.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyVitamin D levels in healthy women. Journal of Clinical Endocrinology & Metabolism 88 (1):157-61, 2003.	Cross-sectional or retrospective assessment of diet after disease diagnosis
August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. American Journal of Obstetrics & Gynecology. 191(5):1666-72, 2004 Nov.	>=20% subjects with diseases
August P, Marcaccio B, Gertner JM, Druzin ML, Resnick LM, Laragh JH. Abnormal 1,25-dihydroxyVitamin D metabolism in preeclampsia. American Journal of Obstetrics & Gynecology 166 (4):1295-9, 1992.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Back O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Dermato -Venereologica 89 (1):28 -32 , 2009.	combination of vit D/Ca and other treatment w/o analysis of independent effect
Bailey BW, Sullivan DK, Kirk EP, Hall S, Donnelly JE. The influence of calcium consumption on weight and fat following 9 months of exercise in men and women. Journal of the American College of Nutrition 2007; 26(4):350-355.	No outcomes of interest
Bakker R, Rifas-Shiman SL, Kleinman KP, Lipshultz SE, Gillman MW. Maternal calcium intake during pregnancy and blood pressure in the offspring at age 3 years: a follow-up analysis of the Project Viva cohort. American Journal of Epidemiology 168 (12):1374 -80 , 2008.	age <18 (BP outcome)
Baron JA, Beach M, Mandel JS et al. Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. Annals of the New York Academy of Sciences 889:138-45, 1999.	Duplicate publication (see Baron 1999 NEJM)
Baron JA, Beach M, Mandel JS et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. . New England Journal of Medicine 340 (2):101-7, 1999.	In Weigarten 2008 systematic review
Baron JA, Tosteson TD, Wargovich MJ et al. Calcium supplementation and rectal mucosal proliferation: a randomized controlled trial. . Journal of the National Cancer Institute 87 (17):1303-7, 1995.	No outcomes of interest
Barr SI. Calcium and body fat in peripubertal girls: cross-sectional and longitudinal observations. Obesity 2007; 15(5):1302-1310.	Not RCT growth study
Barsoum GH, Hendrickse C, Winslet MC et al. Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. British Journal of Surgery 79 (6):581-3, 1992.	No outcomes of interest

Excluded Study	Reason
Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose Vitamin D supplementation on serum Vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine 2006; 1(1):27-35.	In Ottawa EPC report
Belizan JM, Villar J, Bergel E et al. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial.. BMJ 315 (7103):281-5, 1997.	In Hofmeyer 2007 systematic review
Belizan JM, Villar J, Gonzalez L, Campodonico L, Bergel E. Calcium supplementation to prevent hypertensive disorders of pregnancy.. New England Journal of Medicine 325 (20):1399 -405, 1991.	In Hofmeyer 2007 systematic review
Belizan JM, Villar J, Pineda O et al. Reduction of blood pressure with calcium supplementation in young adults. JAMA 249 (9):1161 -5, 1983.	In systematic review
Belizan JM, Villar J, Zalazar A, Rojas L, Chan D, Bryce GF. Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women. American Journal of Obstetrics & Gynecology 146 (2):175 -80, 1983.	In Hofmeyer 2007 systematic review
Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the Vitamin D-endocrine system in obese subjects. Journal of Clinical Investigation 76 (1):370-3, 1985.	Not RCT arrow 4 study
Bell NH, Epstein S, Shary J, Greene V, Oexmann MJ, Shaw S. Evidence of a probable role for 25-hydroxyVitamin D in the regulation of human calcium metabolism. Journal of Bone & Mineral Research 3(5):489-95, 1988.	Not RCT arrow 4 study
Bell NH, Godsen RN, Henry DP, Shary J, Epstein S. The effects of muscle-building exercise on Vitamin D and mineral metabolism. Journal of Bone & Mineral Research 3(4):369-73, 1988.	No outcomes of interest
Bell NH. Hypercalcemic and hypocalcemic disorders: diagnosis and treatment. Nephron 23(2-3):147-51, 1979.	Review paper
Berggren M, Stenvall M, Olofsson B, Gustafson Y. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up. Osteoporosis International 1919;801-9.	100% patients with femoral neck fracture who admitted to the hospital
Berkey CS, Rockett HR, Willett WC, Colditz GA. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents.. Archives of Pediatrics & Adolescent Medicine 159 (6):543 -50, 2005.	Not RCT growth study
Berube S, Diorio C, Masse B et al. Vitamin D and calcium intakes from food or supplements and mammographic breast density. Cancer Epidemiology, Biomarkers & Prevention 14(7):1653-9, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Bierenbaum ML, Fleischman AI, Raichelson RI. Long term human studies on the lipid effects of oral calcium. Lipids 7 (3):202-6, 1972.	No outcomes of interest
Bierenbaum ML, Wolf E, Bisgeier G, Maginnis WP. Dietary calcium. A method of lowering blood pressure. American Journal of Hypertension 1(3 Pt 3):149S -152S, 1988.	In systematic review

Excluded Study	Reason
Bischoff HA, Stahelin HB, Dick W et al. Effects of Vitamin D and calcium supplementation on falls: a randomized controlled trial.. Journal of Bone & Mineral Research 18 (2):343-51, 2003.	In Ottawa EPC report
Bischoff-Ferrari HA, Conzelmann M, Stahelin HB et al. Is fall prevention by Vitamin D mediated by a change in postural or dynamic balance? Osteoporosis International 2006; 17(5):656-663.	Secondary analysis of an original RCT by Bischoff-Ferrari 2003, which is already in Ottawa's report
Bischoff-Ferrari HA, Orav EJ, wson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Archives of Internal Medicine 166 (4):424-30, 2006.	In Ottawa EPC report
Blum M, Kirsten M, Worth MH, Jr. Reversible hypertension. Caused by the hypercalcemia of hyperparathyroidism, Vitamin D toxicity, and calcium infusion. JAMA 237 (3):262 -3, 1977.	No 25(OH)D or dietary Ca
Boggess KA, Samuel L, Schmucker BC, Waters J, Easterling TR. A randomized controlled trial of the effect of third-trimester calcium supplementation on maternal hemodynamic function. Obstetrics & Gynecology 90 (2):157-61, 1997.	In Hofmeyer 2007 systematic review
Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. . Lancet 356 (9238):1300-6, 2000.	In Weigarten 2008 systematic review
Bonithon-Kopp C, Piard F, Fenger C et al. Colorectal adenoma characteristics as predictors of recurrence. Diseases of the Colon & Rectum 47 (3):323-33, 2004.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Boon N, Koppes LL, Saris WH, Van MW. The relation between calcium intake and body composition in a Dutch population: The Amsterdam Growth and Health Longitudinal Study. American Journal of Epidemiology 162 (1):27-32, 2005.	No outcomes of interest
Bostick RM, Fosdick L, Grandits GA, Grambsch P, Gross M, Louis TA. Effect of calcium supplementation on serum cholesterol and blood pressure. A randomized, double-blind, placebo-controlled, clinical trial. Archives of Family Medicine 9(1):31-8 2000.	>=20% subjects with diseases
Bostick RM, Fosdick L, Wood JR et al. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial.. Journal of the National Cancer Institute 87 (17):1307-15, 1995.	No outcomes of interest
Bostick RM, Potter JD, Fosdick L et al. Calcium and colorectal epithelial cell proliferation: a preliminary randomized, double-blinded, placebo-controlled clinical trial. Journal of the National Cancer Institute. 85(2):132-41, 1993 Jan 20.	No outcomes of interest
Boutron MC, Faivre J, Marteau P, Couillault C, Senesse P, Quipourt V. Calcium, phosphorus, Vitamin D, dairy products and colorectal carcinogenesis: a French case--control study.. British Journal of Cancer 74 (1):145-51, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Bowen J, Noakes M, Clifton PM. Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. International Journal of Obesity 29 (8):957-65, 2005.	In systematic review
Braverman AS. Evidence that high calcium and Vitamin D intake decrease the risk of breast cancer in premenopausal women: implications for breast cancer prevention and screening. Southern Medical Journal 100 (11):1061-2, 2007.	Review paper
Brekke HK, Ludvigsson J. Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study. Pediatric Diabetes 2007; 8(1):11-14.	No 25(OH)D or dietary Ca
Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of Vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. Journal of the American Geriatrics Society 2007; 55(2):234-239.	In Ottawa EPC report
Brooke OG, Butters F, Wood C. Intrauterine Vitamin D nutrition and postnatal growth in Asian infants. British Medical Journal Clinical Research Ed 283 (6298):1024, 1981.	No 25(OH)D or dietary Ca
Brooke OG. Supplementary Vitamin D in infancy and childhood. Archives of Disease in Childhood 1983; 58(8):573-574.	Review paper
Brunvand L, Quigstad E, Urdal P, Haug E. Vitamin D deficiency and fetal growth. Early Human Development 45 (1-2):27-33, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Brunvand L, Shah SS, Bergstrom S, Haug E. Vitamin D deficiency in pregnancy is not associated with obstructed labor. A study among Pakistani women in Karachi. Acta Obstetricia et Gynecologica Scandinavica 77 (3):303-6, 1998.	No outcomes of interest
Campbell CG, Chew BP, Luedecke LO, Shultz TD. Yogurt consumption does not enhance immune function in healthy premenopausal women. Nutrition & Cancer 37 (1):27-35, 2000.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Cancela L, Le BN, Miravet L. Relationship between the Vitamin D content of maternal milk and the Vitamin D status of nursing women and breast-fed infants. Journal of Endocrinology 110 (1):43-50, 1986.	Not RCT arrow 4 study
Canto-Costa MH, Kunii I, Hauache OM. Body fat and cholecalciferol supplementation in elderly homebound individuals. Brazilian Journal of Medical & Biological Research 39 (1):91-8, 2006.	Not RCT arrow 4 study
Caplan RH, Miller CD, Silva PD. Severe hypercalcemia in a lactating woman in association with moderate calcium carbonate supplementation: a case report. Journal of Reproductive Medicine 49 (3):214-7, 2004.	Case report
Cappuccio FP, Elliott P, Allender PS, Pryer J, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. . American Journal of Epidemiology 142 (9):935-45, 1995.	Meta-analysis
Carlon GC, Howland WS, Goldiner PL, Kahn RC, Bertoni G, Turnbull AD. Adverse effects of calcium administration. Report of two cases. Archives of Surgery 113 (7):882-5, 1978.	Case report

Excluded Study	Reason
Carlson LA, Derblom H, Lanner A. Effect of different doses of Vitamin D on serum cholesterol and triglyceride levels in healthy men. Atherosclerosis 12 (2):313-7, 1970.	Multiple antioxidant trials analyses
Caruso JB, Patel RM, Julka K, Parish DC. Health-behavior induced disease: return of the milk-alkali syndrome. Journal of General Internal Medicine 2007; 22(7):1053-1055.	Case report
Cats A, Kleibeuker JH, van der MR et al. Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. Journal of the National Cancer Institute 87 (8):598-603, 1995.	No outcomes of interest
Cervellin G, Bonino P, Palummeri E, Passeri M. Calcium phosphate and blood pressure: their relationships in a geriatric population. American Journal of Nephrology 6 Suppl 1:16-8, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. American Journal of Clinical Nutrition 36 (3):438-43, 1982.	In Ottawa EPC report
Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. Journal of Pediatrics 123 (3):439-43, 1993.	>=20% subjects with diseases
Chan JM, Pietinen P, Virtanen M et al. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland). Cancer Causes & Control 11(9):859-67, 2000.	Superseded by Mitrou 2007
Chen W, Dawsey SM, Qiao YL et al. Prospective study of serum 25(OH)-Vitamin D concentration and risk of oesophageal and gastric cancers. British Journal of Cancer 2007; 97(1):123-128.	No outcomes of interest
Chyou PH, Nomura AM, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. International Journal of Cancer 60 (5):616-21, 1995.	No outcomes of interest
Cleghorn GJ, Tudehope DI. Neonatal intestinal obstruction associated with oral calcium supplementation. Australian Paediatric Journal 17(4):298-9, 1981.	Case report
Cockburn F, Belton NR, Purvis RJ et al. Maternal Vitamin D intake and mineral metabolism in mothers and their newborn infants. British Medical Journal 281 (6232):11-4, 1980.	Not RCT arrow 4 study
Cohen GR, Curet LB, Levine RJ et al. Ethnicity, nutrition, and birth outcomes in nulliparous women. American Journal of Obstetrics & Gynecology 2001; 185(3):660-667.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. American Journal of Clinical Nutrition 55 (5):1018 -23, 1992.	No outcomes of interest
Combs GF, Jr., Hassan N, Dellagana N et al. Apparent efficacy of food-based calcium supplementation in preventing rickets in Bangladesh. Biological Trace Element Research 121 (3):193 -204, 2008.	>=20% subjects with diseases

Excluded Study	Reason
Cong K, Chi S, Liu G. Calcium supplementation during pregnancy for reducing pregnancy induced hypertension. Chinese Medical Journal 108 (1):57-9, 1995.	In Hofmeyer 2007 systematic review
Corless D, Dawson E, Fraser F et al. Do Vitamin D supplements improve the physical capabilities of elderly hospital patients? Age & Ageing 14(2):76-84, 1985.	In Ottawa EPC report
Cosman F, Nieves J, Shen V, Lindsay R. Oral 1,25-dihydroxyVitamin D administration in osteoporotic women: effects of estrogen therapy. Journal of Bone & Mineral Research 10(4):594-600, 1995.	Not RCT arrow 4 study
Costenbader KH, Feskanich D, Holmes M, Karlson EW, ito-Garcia E. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Annals of the Rheumatic Diseases 67 (4):530-5, 2008.	Observational study estimated Vitamin D supplement doses
Crowther CA, Hiller JE, Pridmore B et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial. FRACOG and the ACT Study Group. Australian & New Zealand Journal of Obstetrics & Gynaecology 39 (1):12-8, 1999.	In Hofmeyer 2007 systematic review
Dahifar H, Faraji A, Yassobi S, Ghorbani A. Asymptomatic rickets in adolescent girls. Indian Journal of Pediatrics 2007; 74(6):571-575.	Not RCT arrow 4 study
Dattani JT, Exton-Smith AN, Stephen JM. Vitamin D status of the elderly in relation to age and exposure to sunlight. Human Nutrition - Clinical Nutrition 38 (2):131-7, 1984.	Not RCT arrow 4 study
Dauchet L, Kesse-Guyot E, Czernichow S et al. Dietary patterns and blood pressure change over 5-y follow-up in the SU.VI.MAX cohort. American Journal of Clinical Nutrition 2007; 85(6):1650-1656.	No 25(OH)D or dietary Ca
Davie MW, Abraham RR, Hewins B, Wynn V. Changes in bone and muscle constituents during dieting for obesity. Clinical Science 70 (3):285-93, 1986.	No outcomes of interest
Davies KM, Heaney RP, Recker RR et al. Calcium intake and body weight. Journal of Clinical Endocrinology & Metabolism 85 (12):4635-8, 2000.	Meta-analysis; five clinical studies
Deheeger M, Bellisle F, Rolland-Cachera MF. The French longitudinal study of growth and nutrition: data in adolescent males and females. Journal of Human Nutrition & Dietetics 15 (6):429-38, 2002.	Analysis did not relate exposure to outcome
DeJongh ED, Binkley TL, Specker BL. Fat mass gain is lower in calcium-supplemented than in unsupplemented preschool children with low dietary calcium intakes. American Journal of Clinical Nutrition 84 (5):1123-7, 2006.	<9y (a study on BMI)
Dent CE, Gupta MM. Plasma 25-hydroxyVitamin-D-levels during pregnancy in Caucasians and in vegetarian and non-vegetarian Asians. Lancet 2(7944):1057-60, 1975.	No outcomes of interest
DeSantiago S, Alonso L, Halhali A, Larrea F, Isoard F, Bourges H. Negative calcium balance during lactation in rural Mexican women. American Journal of Clinical Nutrition 76 (4):845-51, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Devereux G, Litonjua AA, Turner SW et al. Maternal Vitamin D intake during pregnancy and early childhood wheezing. American Journal of Clinical Nutrition 2007; 85(3):853-859.	No 25(OH)D or dietary Ca
Dewey KG, Lonnerdal B. Milk and nutrient intake of breast-fed infants from 1 to 6 months: relation to growth and fatness. Journal of Pediatric Gastroenterology & Nutrition 2(3):497 -506, 1983.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Dhesi JK, Bearne LM, Moniz C et al. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with Vitamin D status. Journal of Bone & Mineral Research 17(5):891-7, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Dhesi JK, Jackson SH, Bearne LM et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age & Ageing 33 (6):589-95, 2004.	Intramuscular injection of high dose ergocalciferol
Dijkstra SH, van BA, Janssen JW, de Vleeschouwer LH, Huysman WA, van den Akker EL. High prevalence of Vitamin D deficiency in newborn infants of high-risk mothers.[erratum appears in Arch Dis Child. 2007 Nov;92(11):1049]. Archives of Disease in Childhood 2007; 92(9):750-753.	Relationship betweem mother's 25(OH)D and infant's 25(OH)D levels
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. Obesity Research 13(10):1727-38, 2005.	Outcome is BW but participants age is from 4 to 10y (mostly <9y)
Dobnig H, Pilz S, Scharnagl H et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Archives of Internal Medicine 168 (12):1340 -9 , 2008.	>=20% subjects with diseases
Doege C, Bauer J. Effect of high volume intake of mother's milk with an individualized supplementation of minerals and protein on early growth of preterm infants <28 weeks of gestation. Clinical Nutrition 26 (5):581-8, 2007.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Domrongkitchaiporn S, Ongphiphadhanakul B, Stitchantrakul W et al. Risk of calcium oxalate nephrolithiasis after calcium or combined calcium and calcitriol supplementation in postmenopausal women. Osteoporosis International 11(6):486-92, 2000.	No outcomes of interest, no UL outcomes
Drinka PJ, Nolten WE. Hazards of treating osteoporosis and hypertension concurrently with calcium, Vitamin D, and distal diuretics. Journal of the American Geriatrics Society 32 (5):405-7, 1984.	Case report
Drouillet P, Balkau B, Charles MA et al. Calcium consumption and insulin resistance syndrome parameters. Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Nutrition Metabolism & Cardiovascular Diseases 2007; 17(7):486-492.	No outcomes of interest
Ehrenberg A. Non-medical prevention of pre-eclampsia. Acta Obstetricia et Gynecologica Scandinavica - Supplement 164:108-10, 1997.	Review paper
Epstein S, Bell NH, Shary J, Shaw S, Greene A, Oexmann MJ. Evidence that obesity does not influence the Vitamin D-endocrine system in blacks. Journal of Bone & Mineral Research 1(2):181-4, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Epstein S, Stern PH, Bell NH, Dowdeswell I, Turner RT. Evidence for abnormal regulation of circulating 1 alpha, 25-dihydroxyVitamin D in patients with pulmonary tuberculosis and normal calcium metabolism. Calcified Tissue International 36 (5):541-4, 1984.	Not RCT arrow 4 study
Ertbeg P, Norgaard P, Bang L, Nyholm H, Rudnicki M. Ionized magnesium in gestational diabetes. Magnesium Research 17(1):35-8, 2004.	No 25(OH)D or dietary Ca
Faivre J, Couillault C, Kronborg O et al. Chemoprevention of metachronous adenomas of the large bowel: design and interim results of a randomized trial of calcium and fibre. ECP Colon Group. European Journal of Cancer Prevention 6(2):132-8, 1997.	Design and interim results article
Farrerons J, Barnadas M, Rodriguez J et al. Clinically prescribed sunscreen (sun protection factor 15) does not decrease serum Vitamin D concentration sufficiently either to induce changes in parathyroid function or in metabolic markers. British Journal of Dermatology 139 (3):422-7, 1998.	No outcomes of interest
Faulkner KA, Cauley JA, Zmuda JM et al. Higher 1,25-dihydroxyVitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporosis International 2006; 17(9):1318-1328.	In Ottawa EPC report
Feeley RM, Eitenmiller RR, Jones JB, Jr., Barnhart H. Calcium, phosphorus, and magnesium contents of human milk during early lactation. Journal of Pediatric Gastroenterology & Nutrition 2(2):262-7, 1983.	No outcomes of interest
Felson DT, Niu J, Clancy M et al. Low levels of Vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis & Rheumatism 2007; 56(1):129-136.	No outcomes of interest
Fleischman AR, Rosen JF, Cole J, Smith CM, DeLuca HF. Maternal and fetal serum 1,25-dihydroxyVitamin D levels at term. Journal of Pediatrics 1980; 97(4):640-642.	No outcomes of interest
Fleischman AR, Rosen JF, Nathenson G. 25-hydroxyVitamin D. Serum levels and oral administration of calcifediol in neonates. Archives of Internal Medicine 138 Spec No: 869-73, 1978.	Premature infants
Forman JP, Bischoff-Ferrari HA, Willett WC, Stampfer MJ, Curhan GC. Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies. Hypertension 46 (4):676-82, 2005.	No 25(OH)D or dietary Ca
Franco A, Sikalidis AK, Solis Herruzo JA. Colorectal cancer: influence of diet and lifestyle factors. Revista Espanola de Enfermedades Digestivas 97 (6):432-48, 2005.	Review paper
Freedman DM, Tangrea JA, Virtamo J, Albanes D. The effect of beta-carotene supplementation on serum Vitamin D metabolite concentrations. Cancer Epidemiology, Biomarkers & Prevention 8 (12):1115-6, 1999.	No outcomes of interest
Fronczak CM, Baron AE, Chase HP et al. In utero dietary exposures and risk of islet autoimmunity in children. Diabetes Care 26 (12):3237 -42 , 2003.	Observational study estimated Vitamin D supplement doses

Excluded Study	Reason
Galloe AM, Graudal N, Moller J, Bro H, Jorgensen M, Christensen HR. Effect of oral calcium supplementation on blood pressure in patients with previously untreated hypertension: a randomised, double-blind, placebo-controlled, crossover study. Journal of Human Hypertension 7 (1):43-5, 1993.	In systematic review
Gambacciani M, Ciaponi M, Cappagli B et al. Body weight, body fat distribution, and hormonal replacement therapy in early postmenopausal women.[erratum appears in J Clin Endocrinol Metab 1997 Dec;82(12):4074]. Journal of Clinical Endocrinology & Metabolism 82 (2):414-7, 1997.	No outcomes of interest
Garland CF, Garland FC. Do sunlight and Vitamin D reduce the likelihood of colon cancer? [reprint in Int J Epidemiol. 2006 Apr;35(2):217-20; PMID: 16303809]. International Journal of Epidemiology 9 (3):227-31, 1980.	Ecological study
Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC. Role of ultraviolet B irradiance and Vitamin D in prevention of ovarian cancer. American Journal of Preventive Medicine 2006; 31(6):512-514.	No 25(OH)D or dietary Ca
Genkinger JM, Hunter DJ, Spiegelman D et al. Dairy products and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiology, Biomarkers & Prevention 15 (2):364-72, 2006.	Pooled analysis
Gertner JM, Domenech M. 25-HydroxyVitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. Journal of Clinical Pathology 30(2):144-50, 1977.	>=20% subjects with diseases
Gillies DR, Hay A, Sheltawy MJ, Congdon PJ. Effect of phototherapy on plasma 25(OH)-Vitamin D in neonates. Biology of the Neonate 1984; 45(5):225-227.	Not RCT arrow 4 study
Gillman MW, Oliveria SA, Moore LL, Ellison RC. Inverse association of dietary calcium with systolic blood pressure in young children. JAMA 267 (17):2340-3, 1992.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Gillman MW, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Lipshultz SE. Maternal calcium intake and offspring blood pressure. Circulation 110 (14):1990-5, 2004.	Relationship between maternal intake and offspring blood pressure
Giovannucci E, Liu Y, Rimm EB et al. Prospective study of predictors of Vitamin D status and cancer incidence and mortality in men.. Journal of the National Cancer Institute 98 (7):451-9, 2006.	Superseded by Giovannucci 2007
Giovannucci E, Rimm EB, Wolk A et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Research 58 (3):442-7, 1998.	Predictive model was used to predict 25(OH)D levels of whole cohort
Giovannucci E, Stampfer MJ, Colditz GA et al. MultiVitamin use, folate, and colon cancer in women in the Nurses' Health Study.. Annals of Internal Medicine 129 (7):517 -24, 1998.	No 25(OH)D or dietary Ca
Gonzalez AJ, White E, Kristal A, Littman AJ. Calcium intake and 10-year weight change in middle-aged adults. Journal of the American Dietetic Association 106 (7):1066-73 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Goswami R, Gupta N, Ray D, Singh N, Tomar N. Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. British Journal of Nutrition 100 (3):526 -9 , 2008.	not RCT curve 4 study
Grady D, Halloran B, Cummings S et al. 1,25-DihydroxyVitamin D3 and muscle strength in the elderly: a randomized controlled trial. Journal of Clinical Endocrinology & Metabolism 73 (5):1111-7, 1991.	1,25(OH)2D supplement
Grant WB. The likely role of Vitamin D from solar ultraviolet-B irradiance in increasing cancer survival. Anticancer Research 26 (4A):2605-14, 2006.	Ecological study
Grau MV, Baron JA, Barry EL et al. Interaction of calcium supplementation and nonsteroidal anti-inflammatory drugs and the risk of colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 14(10):2353-8, 2005.	In Weigarten 2008 systematic review
Greene MF. Trial of calcium to prevent preeclampsia. Journal of Women's Health 6(4):485-6, 1997.	Commentary
Greer FR, Ho M, Dodson D, Tsang RC. Lack of 25-hydroxyVitamin D and 1,25-dihydroxyVitamin D in human milk. Journal of Pediatrics 99 (2):233-5, 1981.	No 25(OH)D or dietary Ca
Greer FR, Hollis BW, Cripps DJ, Tsang RC. Effects of maternal ultraviolet B irradiation on Vitamin D content of human milk. Journal of Pediatrics 105 (3):431-3, 1984.	No 25(OH)D or dietary Ca
Greer FR, Marshall S. Bone mineral content, serum Vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without Vitamin D2 supplements. Journal of Pediatrics 114 (2):204-12, 1989.	In Ottawa EPC report
Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyVitamin D concentration in breast-fed infants with and without supplemental Vitamin D. Journal of Pediatrics 98 (5):696-701, 1981.	In Ottawa EPC report
Gruson M, Cancela L, Denne MA, Miravet L. Relationship between bone GLA-protein (BGP) and calcidiol (25-hydroxycalciferol) in serum of breast-fed infants. Endocrinologia Experimentalis. 20(2-3):329-34, 1986 Aug.	25(OH)D supplement
Gunther CW, Legowski PA, Lyle RM et al. Dairy products do not lead to alterations in body weight or fat mass in young women in a 1-y intervention. American Journal of Clinical Nutrition 81 (4):751-6, 2005.	In systematic review
Gunther CW, Legowski PA, Lyle RM et al. Parathyroid hormone is associated with decreased fat mass in young healthy women. International Journal of Obesity 30 (1):94-9, 2006.	Ca intake and BW measured but not assessed ==> no relevant results reported
Haddad JG, Jr., Rojanasathit S. Acute administration of 25-hydroxycholecalciferol in man. Journal of Clinical Endocrinology & Metabolism 42 (2):284 -90, 1976.	Not RCT arrow 4 study
Hakala P, Karvetti RL. Weight reduction on lactovegetarian and mixed diets. Changes in weight, nutrient intake, skinfold thicknesses and blood pressure. European Journal of Clinical Nutrition 43 (6):421-30, 1989.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Halhali A, Villa AR, Madrazo E et al. Longitudinal changes in maternal serum 1,25-dihydroxyVitamin D and insulin like growth factor I levels in pregnant women who developed preeclampsia: comparison with normotensive pregnant women. Journal of Steroid Biochemistry & Molecular Biology 89 -90 (1-5):553-6, 2004.	No outcomes of interest
Hamet P, Mongeau E, Lambert J et al. Interactions among calcium, sodium, and alcohol intake as determinants of blood pressure. Hypertension 17(1 Suppl):I150-4, 1991.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hamid Z, Riggs A, Spencer T, Redman C, Bodenner D. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed Vitamin D.. Journal of the American Medical Directors Association 2007; 8(2):71-75.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Engelke JA, Shafer MM. Vitamin D insufficiency: disease or no disease? Journal of Bone & Mineral Research 23(7):1052-60, 2008.	Not RCT arrow 4 study
Haub MD, Simons TR, Cook CM, Remig VM, Al-Tamimi EK, Holcomb CA. Calcium-fortified beverage supplementation on body composition in postmenopausal women. Nutrition Journal 4:21, 2005.	In systematic review
Heilbrun LK, Hankin JH, Nomura AM, Stemmermann GN. Colon cancer and dietary fat, phosphorus, and calcium in Hawaiian-Japanese men. American Journal of Clinical Nutrition 43 (2):306-9, 1986.	Letter to the editor
Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN. Dietary Vitamin D and calcium and risk of colorectal cancer. Lancet 1985; 1(8434):925.	Superceded by Stemmermann, 1990 RefID 1691
Herrera JA, revalo-Herrera M, Herrera S. Prevention of preeclampsia by linoleic acid and calcium supplementation: a randomized controlled trial. Obstetrics & Gynecology 91 (4):585 -90, 1998.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Herrmann U, Schwille PO, Schmiedl A, Fan J, Manoharan M. Acute effects of calcium sodium citrate supplementation of a test meal on mineral homeostasis, oxalate, and calcium oxalate crystallization in the urine of healthy humans--preliminary results in patients with idiopathic calcium urolithiasis. Biomedicine & Pharmacotherapy 53 (5-6):264-73, 1999.	No UL outcomes: CaOx crystallization; saturation of CaOx
Hill KM, Braun M, Kern M et al. Predictors of calcium retention in adolescent boys. Journal of Clinical Endocrinology & Metabolism 93 (12):4743 -8 , 2008.	no outcomes of interest
Hiller JE, Crowther CA, Moore VA, Willson K, Robinson JS. Calcium supplementation in pregnancy and its impact on blood pressure in children and women: follow up of a randomised controlled trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 2007; 47(2):115-121.	No outcomes of interest
Hillman LS, Haddad JG. Perinatal Vitamin D metabolism. II. Serial 25-hydroxyVitamin D concentrations in sera of term and premature infants. Journal of Pediatrics 1975; 86(6):928-935.	No clear Vitamin D dose for term infants

Excluded Study	Reason
Hillman LS, Johnson LS, Lee DZ, Vieira NE, Yergey AL. Measurement of true absorption, endogenous fecal excretion, urinary excretion, and retention of calcium in term infants by using a dual-tracer, stable-isotope method. Journal of Pediatrics 1993; 123(3):444-456.	All neonates included weighed < 1500 gm
Hintzpeter B, Mensink GB, Thierfelder W, Muller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. European Journal of Clinical Nutrition 62 (9):1079 -89 , 2008.	cross-sectional or retrospective assessment of diet after disease diagnosis
Hofmeyr GJ, Mlokoti Z, Nikodem VC et al. Calcium supplementation during pregnancy for preventing hypertensive disorders is not associated with changes in platelet count, urate, and urinary protein: a randomized control trial. Hypertension in Pregnancy 27 (3):299 -304 , 2008.	ancillary study (small sample) of WHO trial. The preeclampsia data of WHO trial was already included in the previous SR (Hofmeyer2007).
Hofstad B, Almendingen K, Vatn M et al. Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. Digestion 59 (2):148-56, 1998.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Hofstad B, Vatn MH, Andersen SN, Owen RW, Larsen S, Osnes M. The relationship between faecal bile acid profile with or without supplementation with calcium and antioxidants on recurrence and growth of colorectal polyps. European Journal of Cancer Prevention 7 (4):287-94, 1998.	No independent Ca effect
Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypoVitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004; 80(6 Suppl):1752S-1758S.	In Ottawa EPC report
Hollis JH, Mattes RD. Effect of increased dairy consumption on appetitive ratings and food intake. [erratum appears in Obesity (Silver Spring). 2007 Oct;15(10):2520]. Obesity 2007; 15(6):1520-1526.	No outcomes of interest
Holt PR, Atillasoy EO, Gilman J et al. Modulation of abnormal colonic epithelial cell proliferation and differentiation by low-fat dairy foods: a randomized controlled trial. . JAMA 280 (12):1074-9, 1998.	No outcomes of interest
Holt PR, Bresalier RS, Ma CK et al. Calcium plus Vitamin D alters preneoplastic features of colorectal adenomas and rectal mucosa. Cancer 106 (2):287-96, 2006.	No outcomes of interest
Holt PR, Wolper C, Moss SF, Yang K, Lipkin M. Comparison of calcium supplementation or low-fat dairy foods on epithelial cell proliferation and differentiation. Nutrition & Cancer 41 (1-2):150-5, 2001.	No outcomes of interest
Hunt CD, Johnson LK. Calcium requirements: new estimations for men and women by cross-sectional statistical analyses of calcium balance data from metabolic studies. American Journal of Clinical Nutrition 2007; 86(4):1054-1063.	Arrow 4: calcium balance
Hvarfner A, Ljunghall S, Morlin C, Wide L. Calcium metabolism and arterial blood pressure in a healthy population sample and in hypertensive men. American Journal of Nephrology 6 Suppl 1:14-5, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hyman J, Baron JA, Dain BJ et al. Dietary and supplemental calcium and the recurrence of colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 7 (4):291-5, 1998.	Multiple antioxidant trials analyses

Excluded Study	Reason
Hypponen E, Hartikainen AL, Sovio U, Jarvelin MR, Pouta A. Does Vitamin D supplementation in infancy reduce the risk of pre-eclampsia? European Journal of Clinical Nutrition 2007; 61(9):1136-1139.	Observational study estimated Vitamin D supplement doses
Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of Vitamin D and risk of type 1 diabetes: a birth-cohort study.. Lancet 358 (9292):1500-3, 2001.	Observational study estimated Vitamin D supplement doses
Hypponen E, Sovio U, Wjst M et al. Infant Vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Annals of the New York Academy of Sciences 1037:84-95, 2004.	Observational study estimated Vitamin D supplement doses
Ilich-Ernst JZ, McKenna AA, Badenhop NE et al. Iron status, menarche, and calcium supplementation in adolescent girls.[erratum appears in Am J Clin Nutr 1999 Mar;69(3):577]. American Journal of Clinical Nutrition 68 (4):880-7, 1998.	Ca intake, BMI, LBM and BW measured, but the analyses on the relationship among these were not performed.
Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. Journal of Clinical Endocrinology & Metabolism 93 (9):3430 -5, 2008.	arrow 4 RCT but daily doses were the same in the comparison groups (comparison of daily, weekly versus monthly dose)
Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and Vitamin D3 in an antenatal protocol. International Journal of Gynaecology & Obstetrics 47 (2):115 -20, 1994.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Jackson RD, Donepudi S, Mysiw WJ. Epidemiology of fracture risk in the Women's Health Initiative. Current Osteoporosis Reports 6 (4):155 -61 , 2008.	review paper
Jackson RD, Lacroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-Vitamin D trial: overview and baseline characteristics of participants. Annals of Epidemiology 13(9 Suppl):S98-106, 2003.	Overview of trial participants
Jackson RD, Lacroix AZ, Gass M et al. Calcium plus Vitamin D supplementation and the risk of fractures.[erratum appears in N Engl J Med. 2006 Mar 9;354(10):1102]. New England Journal of Medicine 354 (7):669-83, 2006.	Same as Wactawski-Wende 2006 RefID 1967 in which longer f/up data reported
Jacobs D. Calcium and myocardial infarction. South African Medical Journal Suid -Afrikaanse Tydskrif Vir Geneeskunde 48 (13):523-7, 1974.	No 25(OH)D or dietary Ca
Jacobs ET, Alberts DS, Benuzillo J, Hollis BW, Thompson PA, Martinez ME. Serum 25(OH)D levels, dietary intake of Vitamin D, and colorectal adenoma recurrence. Journal of Steroid Biochemistry & Molecular Biology 2007; 103(3-5):752-756.	Analyses include 25(OH)D measurements taken after outcome (colorectal polyps) occurred.
Jacques PF, Felson DT, Tucker KL et al. Plasma 25-hydroxyVitamin D and its determinants in an elderly population sample. American Journal of Clinical Nutrition 66 (4):929-36, 1997.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Joffe GM, Esterlitz JR, Levine RJ et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. Calcium for Preeclampsia Prevention (CPEP) Study Group.. American Journal of Obstetrics & Gynecology 179 (4):1032-7, 1998.	No 25(OH)D or dietary Ca

Excluded Study	Reason
John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. . Journal of Steroid Biochemistry & Molecular Biology 89 -90 (1-5):549 -52, 2004.	No 25(OH)D or dietary Ca
John WG, Noonan K, Mannan N, Boucher BJ. HypoVitaminosis D is associated with reductions in serum apolipoprotein A-I but not with fasting lipids in British Bangladeshis. American Journal of Clinical Nutrition 82 (3):517-22, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Johnson MA, Fischer JG, Park S. Vitamin D deficiency and insufficiency in the Georgia Older Americans Nutrition Program. Journal of Nutrition for the Elderly 27 (1-2):29 -46 , 2008.	combination of vit D/Ca and other treatment w/o analysis of independent effect
Johnson NE, Smith EL, Freudenheim JL. Effects on blood pressure of calcium supplementation of women. American Journal of Clinical Nutrition 42 (1):12-7, 1985.	In systematic review
Jones G, Scott F. Low bone mass in premenopausal parous women: identification and the effect of an information and bone density feedback program. . Journal of Clinical Densitometry 2(2):109-15, 1999.	No outcomes of interest
Jorde R, Bonaa KH. Calcium from dairy products, Vitamin D intake, and blood pressure: the Tromso Study.. American Journal of Clinical Nutrition 71 (6):1530-5, 2000.	No outcomes of interest
Kampman E, Giovannucci E, van ', V et al. Calcium, Vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. Am J Epidemiol 1994; 139(1):16-29.	Same cohorts as Wu 2002 RefID 529 (HPFS & NHS) and same exposure-outcome relationship but shorter follow-up
Karanja N, Morris CD, Illingworth DR, McCarron DA. Plasma lipids and hypertension: response to calcium supplementation. American Journal of Clinical Nutrition 45 (1):60-5, 1987.	No outcomes of interest
Karanja N, Morris CD, Rufolo P, Snyder G, Illingworth DR, McCarron DA. Impact of increasing calcium in the diet on nutrient consumption, plasma lipids, and lipoproteins in humans. . American Journal of Clinical Nutrition 59 (4):900-7, 1994.	No outcomes of interest
Kawano Y. Role of blood pressure monitoring in non-pharmacological management of hypertension. Blood Pressure Monitoring 7 (1):51-4, 2002.	Review paper
Kearney J, Giovannucci E, Rimm EB et al. Calcium, Vitamin D, and dairy foods and the occurrence of colon cancer in men. American Journal of Epidemiology 143 (9):907-17, 1996.	Longer followup data were published in Wu 2002
Kemi VE, Karkkainen MU, Karp HJ, Laitinen KA, Lamberg-Allardt CJ. Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose-response study in healthy females. British Journal of Nutrition 99 (4):832-9, 2008.	No outcomes of interest
Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 57 (5):M321-5, 2002.	No 25(OH)D or dietary Ca

Excluded Study	Reason
Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of Vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. Journal of the American Geriatrics Society 51 (12):1762-7, 2003.	In Ottawa EPC report
Kesteloot H, Geboers J. Calcium and blood pressure. Lancet 1(8276):813 -5, 1982.	No 25(OH)D or dietary Ca
Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. New England Journal of Medicine 316 (5):235-40, 1987.	Continuous Ca intake analysis only
Kigutha HN, van Staveren WA, Wijnhoven TM, Hautvast JG. Maternal nutritional status may be stressed by seasonal fluctuations in food availability: evidence from rural women in Kenya. International Journal of Food Sciences & Nutrition 46 (3):247-55, 1995.	Ca intake, BMI and BW measured, but analysis did not relate Ca intake to BMI/BW.
Knekt P, Laaksonen M, Mattila C et al. Serum Vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology. 19(5):666-71, 2008 Sep.	No outcomes of interest
Knight KB, Keith RE. Calcium supplementation on normotensive and hypertensive pregnant women. American Journal of Clinical Nutrition 55 (4):891-5, 1992.	No outcomes of interest
Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet 1(7818):1465-7, 1973.	Analysis @ region level, not individual level
Kobayashi E, Okubo Y, Suwazono Y et al. Association between urinary calcium excretion level and mortality in inhabitants of the Jinzu River basin area of Japan. Biological Trace Element Research 89(2):145-53, 2002.	No 25(OH)D or dietary Ca
Koh-Banerjee PK, Ferreira MP, Greenwood M et al. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. Nutrition 21(3):312-9, 2005.	No 25(OH)D or dietary Ca
Kokot F, Pietrek J, Srokowska S et al. 25-hydroxyVitamin D in patients with essential hypertension. Clinical Nephrology 16 (4):188-92, 1981.	On drug Rx for hypertension
Koralek DO, Bertone-Johnson ER, Leitzmann MF et al. Relationship between calcium, lactose, Vitamin D, and dairy products and ovarian cancer. Nutrition & Cancer 2006; 56(1):22-30.	No outcomes of interest
Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R, Thompson IM. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. Cancer 106 (2):320-8, 2006.	No outcomes of interest
Kromhout D, Bosschieter EB, Coulander CD. Potassium, calcium, alcohol intake and blood pressure: the Zutphen Study. American Journal of Clinical Nutrition 41 (6):1299-304, 1985.	No outcomes of interest
Kulier R, de OM, Gulmezoglu AM, Villar J. Nutritional interventions for the prevention of maternal morbidity. International Journal of Gynaecology & Obstetrics 63 (3):231-46, 1998.	SR of prevention of maternal morbidity

Excluded Study	Reason
Kumar R, Cohen WR, Silva P, Epstein FH. Elevated 1,25-dihydroxyVitamin D plasma levels in normal human pregnancy and lactation. Journal of Clinical Investigation 63 (2):342-4, 1979.	No outcomes of interest
Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women. Bone 44 (1):168 -72 , 2009.	>=20% subjects with diseases
Kynast-Gales SA, Massey LK. Effects of dietary calcium from dairy products on ambulatory blood pressure in hypertensive men.. Journal of the American Dietetic Association 92 (12):1497-501, 1992.	In systematic review
Laaksi I, Ruohola JP, Tuohimaa P et al. An association of serum Vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. American Journal of Clinical Nutrition 86 (3):714-7, 2007.	No outcomes of interest
Lakdawala DR, Widdowson EM. Vitamin-D in human milk. Lancet 1(8004):167-8, 1977.	No outcomes of interest
Lamberg-Allardt C, Larjosto M, Schultz E. 25-HydroxyVitamin D concentrations in maternal and cord blood at delivery and in maternal blood during lactation in Finland. Human Nutrition - Clinical Nutrition 38 (4):261-8, 1984.	Not RCT arrow 4 study
Lancia B, Tedesco M, Sergio G, Tenna M. Anthropometric and nutritional assessment in Italian elderly subjects. Journal of Nutrition, Health & Aging 1(3):174-80, 1997.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP. Vitamin D status in a rural postmenopausal female population. Journal of the American College of Nutrition 2006; 25(5):395-402.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Laraia BA, Bodnar LM, Siega-Riz AM. Pregravid body mass index is negatively associated with diet quality during pregnancy. Public Health Nutrition 2007; 10(9):920-926.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lasco A, Gaudio A, Morini E et al. Effect of long-term treatment with raloxifene on mammary density in postmenopausal women. Menopause 2006; 13(5):787-792.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Latham NK, Anderson CS, Lee A et al. A randomized, controlled trial of quadriceps resistance exercise and Vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). . Journal of the American Geriatrics Society 51 (3):291-9, 2003.	In Ottawa EPC report
Le BN, Cancela L, Miravet L. Calcidiol in human milk. The effect of prohormone on Vitamin D status of breast fed unsupplemented infants. Endocrinologia Experimentalis. 20(2-3):325-8, 1986.	Correlation b/tw breastmilk 25(OH)D with infant's serum 25(OH)D
Lee DC, Lee GY. The use of pamidronate for hypercalcemia secondary to acute Vitamin D intoxication. Journal of Toxicology - Clinical Toxicology 36 (7):719-21, 1998.	Case report
Lee WT, Leung SS, Wang SH et al. Double-blind, controlled calcium supplementation and bone mineral accretion in children accustomed to a low-calcium diet.. American Journal of Clinical Nutrition 60 (5):744 -50, 1994.	In Winzenberg 2007 systematic review, no outcomes of interest

Excluded Study	Reason
Levine AJ, Harper JM, Ervin CM et al. Serum 25-hydroxyVitamin D, dietary calcium intake, and distal colorectal adenoma risk. Nutrition & Cancer 2001; 39(1):35-41.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Levine RJ, Esterlitz JR, Raymond EG et al. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. Controlled Clinical Trials 17(5):442-69, 1996.	Methods for trial
Levine RJ, Hauth JC, Curet LB et al. Trial of calcium to prevent preeclampsia.. New England Journal of Medicine 337 (2):69-76, 1997.	In Hofmeyer 2007 systematic review
Lewandowski S, Rodgers AL. Renal response to lithogenic and anti-lithogenic supplement challenges in a stone-free population group. Journal of Renal Nutrition 14(3):170-9, 2004.	No UL outcomes: saturation of CaOx
Liebman M, Chopin LF, Carter E et al. Factors related to blood pressure in a biracial adolescent female population. Hypertension 8(10):843-50, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lin PH, Appel LJ, Funk K et al. The PREMIER intervention helps participants follow the Dietary Approaches to Stop Hypertension dietary pattern and the current Dietary Reference Intakes recommendations. Journal of the American Dietetic Association 2007; 107(9):1541-1551.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Lin YC, Lyle RM, McCabe LD, McCabe GP, Weaver CM, Teegarden D. Dairy calcium is related to changes in body composition during a two-year exercise intervention in young women. Journal of the American College of Nutrition. 19(6):754-60, 2000 Nov-Dec.	No outcomes of interest
Lind L, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alphacalcidol. A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. Acta Medica Scandinavica 223 (3):211-7, 1988.	>=20% subjects with diseases
Lipkin M, Friedman E, Winawer SJ, Newmark H. Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. Cancer Research 49 (1):248 -54, 1989.	>=20% subjects with diseases
Lipkin M, Newmark H. Effect of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. New England Journal of Medicine 313 (22):1381-4, 1985.	No outcomes of interest
Liu LS. Epidemiology of hypertension and cardiovascular disease--China experience. Clinical & Experimental Hypertension - Part A, Theory & Practice 12 (5):831-44, 1990.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Liu S, Choi HK, Ford E et al. A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care 29 (7):1579-84, 2006.	No 25(OH)D or dietary Ca
Ljunghall S, Lind L, Lithell H et al. Treatment with one-alpha-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance--a prospective randomized double-blind study. Acta Medica Scandinavica 222 (4):361-7, 1987.	>=20% subjects with diseases
Lonzer MD, Imrie R, Rogers D, Worley D, Licata A, Secic M. Effects of heredity, age, weight, puberty, actiVitaminy, and calcium intake on bone mineral density in children. Clinical Pediatrics 35 (4):185-9, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Lopez-Jaramillo P, Delgado F, Jacome P, Teran E, Ruano C, Rivera J. Calcium supplementation and the risk of preeclampsia in Ecuadorian pregnant teenagers. Obstetrics & Gynecology 90 (2):162-7, 1997.	In Hofmeyer 2007 systematic review
Lopez-Jaramillo P, Narvaez M, Weigel RM, Yepez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. British Journal of Obstetrics & Gynaecology 96 (6):648 -55, 1989.	In Hofmeyer 2007 systematic review
Luft FC, Aronoff GR, Sloan RS, Fineberg NS, Weinberger MH. Short-term augmented calcium intake has no effect on sodium homeostasis. Clinical Pharmacology & Therapeutics 39 (4):414-9, 1986.	No outcomes of interest
Lutter CK, Rodriguez A, Fuenmayor G, Avila L, Sempertegui F, Escobar J. Growth and micronutrient status in children receiving a fortified complementary food. Journal of Nutrition 138 (2):379-88, 2008.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Lyle RM. Does baseline serum total calcium level influence the blood pressure response to calcium supplementation? A double-blind study. Netherlands Journal of Medicine 41 (1-2):48-55, 1992.	In systematic review
Lynch MF, Griffin IJ, Hawthorne KM, Chen Z, Hamzo M, Abrams SA. Calcium balance in 1-4-y-old children. American Journal of Clinical Nutrition 2007; 85(3):750-754.	Arrow 4: calcium balance
Ma J, Stampfer MJ, Gann PH et al. Vitamin D receptor polymorphisms, circulating Vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiology, Biomarkers & Prevention 7 (5):385-90, 1998.	Main results had been previous published (Gann 1996, RefID 3783), and no additional usable data
Macdonald HM, New SA, Campbell MK, Reid DM. Longitudinal changes in weight in perimenopausal and early postmenopausal women: effects of dietary energy intake, energy expenditure, dietary calcium intake and hormone replacement therapy. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 27 (6):669-76, 2003.	No outcomes of interest
Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. American Journal of Hypertension 11(1 Pt 1):46-53, 1998.	No outcomes of interest
Malila N, Virtanen M, Pietinen P et al. A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. Nutrition & Cancer 32 (3):146 -53, 1998.	Superseded by Pietinen 1999
Mandic-Puljek M, Mandic ML, Perl A, Kenjeric D. Calcium intake, food sources and seasonal variations in eastern Croatia. Collegium Antropologicum 29 (2):503-7, 2005.	No outcomes of interest
Manios Y, Moschonis G, Grammatikaki E, Katsaroli I, Kanelou P, Tanagra S. Nutrition education in postmenopausal women: changes in dietary and cardiovascular indices. Maturitas 2006; 55(4):338-347.	Nutrition education intervention study
Marangella M, Vitaminale C, Petrarulo M, Rovera L, Dutto F. Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis. Clinical Science 91 (3):313-8, 1996.	No UL outcomes: saturation of CaOx

Excluded Study	Reason
Markestad T, Kolmannskog S, Arntzen E, Toftegaard L, Haneberg B, Aksnes L. Serum concentrations of Vitamin D metabolites in exclusively breast-fed infants at 70 degrees north. Acta Paediatrica Scandinavica 73 (1):29-32, 1984.	No relation with 25(OH)D to growth outcome
Markestad T. Effect of season and Vitamin D supplementation on plasma concentrations of 25-hydroxyVitamin D in Norwegian infants. Acta Paediatrica Scandinavica 72 (6):817-21, 1983.	Not RCT arrow 4 study
Markestad T. Plasma concentrations of Vitamin D metabolites in unsupplemented breast-fed infants. European Journal of Pediatrics 141 (2):77-80, 1983.	No outcomes of interest
Marniemi J, Jarvisalo J, Toikka T, Raiha I, Ahotupa M, Sourander L. Blood Vitamins, mineral elements and inflammation markers as risk factors of vascular and non-vascular disease mortality in an elderly population. International Journal of Epidemiology 27 (5):799-807, 1998.	No 25(OH)D or dietary Ca
Martinez ME, Giovannucci EL, Colditz GA et al. Calcium, Vitamin D, and the occurrence of colorectal cancer among women. Journal of the National Cancer Institute 88 (19):1375-82, 1996.	Longer followup data were published in Wu 2002
Marx SJ, Swart EG, Jr., Hamstra AJ, DeLuca HF. Normal intrauterine development of the fetus of a woman receiving extraordinarily high doses of 1,25-dihydroxyVitamin D3. Journal of Clinical Endocrinology & Metabolism 51 (5):1138 -42, 1980.	Case report
Masse PG, Tranchant CC, Jougleux JL, Coburn SP, Cole DE. Cardiovascular disease-risk factors in middle-aged osteopaenic women treated with calcium alone or combined to three nutrients essential to artery and bone collagen. Journal of Human Nutrition & Dietetics 21(2):117-28, 2008.	No outcomes of interest
Matheson NA. Letter: Multiple sclerosis and diet. Lancet 2 (7884):831, 1974.	Letter to the editor
Matsumoto T, Kubodera N. ED-71, a new active Vitamin D3, increases bone mineral density regardless of serum 25(OH)D levels in osteoporotic subjects. Journal of Steroid Biochemistry & Molecular Biology 2007; 103(3-5):584-586.	Vitamin D analog
Mawer EB, Berry JL, Sommer-Tsilenis E, Beykirch W, Kuhlwein A, Rohde BT. Ultraviolet irradiation increases serum 1,25-dihydroxyVitamin D in Vitamin-D-replete adults. Mineral & Electrolyte Metabolism 10(2):117-21, 1984.	Not RCT arrow 4 study
Mazess RB, Peppler WW, Chesnut CH, III, Nelp WB, Cohn SH, Zanzi I. Total body bone mineral and lean body mass by dual-photon absorptiometry. II. Comparison with total body calcium by neutron activation analysis. Calcified Tissue International 33 (4):361-3, 1981.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Mazess RB, Peppler WW, Harrison JE, McNeill KG. Total body bone mineral and lean body mass by dual-photon absorptiometry. III. Comparison with trunk calcium by neutron activation analysis. Calcified Tissue International 33 (4):365-8, 1981.	No 25(OH)D or dietary Ca

Excluded Study	Reason
McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension. A randomized, double-blind, placebo-controlled, crossover trial. Annals of Internal Medicine 103 (6 (Pt 1)):825 -31, 1985.	In systematic review
Merlino LA, Curtis J, Mikuls TR et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study.. Arthritis & Rheumatism 50(1):72-7, 2004.	Observational study estimated Vitamin D supplement doses
Methy N, Binquet C, Boutron-Ruault MC, Paillot B, Faivre J, Bonithon-Kopp C. Dietary fatty acids and recurrence of colorectal adenomas in a European intervention trial. Nutrition & Cancer 60 (5):560 -7 , 2008.	no 25(OH)D or dietary Ca
Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci E. Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in US men. American Journal of Epidemiology 152 (12):1145-53, 2000.	No outcomes of interest
Misselwitz J, Hesse V, Markestad T. Nephrocalcinosis, hypercalciuria and elevated serum levels of 1,25-dihydroxyVitamin D in children. Possible link to Vitamin D toxicity. Acta Paediatrica Scandinavica 79 (6-7):637-43, 1990.	Case report
Moerman CJ, Smeets FW, Kromhout D. Dietary risk factors for clinically diagnosed gallstones in middle-aged men. A 25-year follow-up study (the Zutphen Study). Annals of Epidemiology 4(3):248-54, 1994.	No outcomes of interest
Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 51 (8):1391 -8 , 2008.	ecological study
Moller UK, Ramlau-Hansen CH, Rejnmark L, Heickendorff L, Henriksen TB, Mosekilde L. Postpartum Vitamin D insufficiency and secondary hyperparathyroidism in healthy Danish women. European Journal of Clinical Nutrition 2006; 60(10):1214-1221.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Morley R, Carlin JB, Dwyer T. Maternal calcium supplementation and cardiovascular risk factors in twin offspring.. International Journal of Epidemiology 33 (6):1304-9, 2004.	No 25(OH)D or dietary Ca
Morosetti M, Jankovic L, Palombo G et al. High-dose calcitriol therapy and progression of cardiac vascular calcifications. Journal of Nephrology 21(4):603 -8 , 2008;-Aug.	i.v. calcitriol
Morris CD, McCarron DA. Effect of calcium supplementation in an older population with mildly increased blood pressure. American Journal of Hypertension 5(4 Pt 1):230-7, 1992.	No outcomes of interest
Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyVitamin D levels and risk of multiple sclerosis. JAMA. 296(23):2832-8, 2006 Dec 20.	No outcomes of interest
Muray S, Marco MP, Craver L, Rue M, Valdivielso JM, Fernandez E. Influence of mineral metabolism parameters on pulse pressure in healthy subjects.. Clinical Nephrology 2006; 66(6):411-417.	No 25(OH)D or dietary Ca

Excluded Study	Reason
Nakamura K, Nishiwaki T, Ueno K, Yamamoto M. Age-related decrease in serum 25-hydroxyVitamin D concentrations in the frail elderly: a longitudinal study. Journal of Bone & Mineral Metabolism 2007; 25(4):232-236.	Effect of aging on 25(OH) D
Nakamura R, Saruta T. Effect of calcium supplementation on blood pressure in essential hypertensive subjects. Japanese Journal of Medicine 26 (2):203-6, 1987.	No outcomes of interest
Nako Y, Fukushima N, Tomomasa T, Nagashima K, Kuroume T. HyperVitaminosis D after prolonged feeding with a premature formula. Pediatrics 1993; 92(6):862-864.	Case report
Narang NK, Gupta RC, Jain MK. Role of Vitamin D in pulmonary tuberculosis. Journal of the Association of Physicians of India 32 (2):185-8, 1984.	No outcomes of interest
Nayir A, Kadioglu A, Sirin A, Emre S, Tonguc E, Bilge I. Causes of increased renal medullary echogenicity in Turkish children. Pediatric Nephrology 9 (6):729 -33, 1995.	Case report
Need AG, O'Loughlin PD, Horowitz M, Nordin BE. Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyVitamin D in postmenopausal women. Clinical Endocrinology 62 (6):738-41, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT. Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. Osteoporosis International 1919;673-9.	not RCT bone study (postmenepausal women)
Nilas L, Christiansen C. Treatment with Vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. International Journal of Obesity 8(5):407-11, 1984.	Review paper
Niromanesh S, Laghaii S, Mosavi-Jarrahi A. Supplementary calcium in prevention of pre-eclampsia. International Journal of Gynaecology & Obstetrics 74 (1):17-21, 2001.	In Hofmeyer 2007 systematic review
Nishimura K, Shima M, Tsugawa N et al. Long-term hospitalization during pregnancy is a risk factor for Vitamin D deficiency in neonates.[erratum appears in J Bone Miner Metab. 2003;21(4):253]. Journal of Bone & Mineral Metabolism 21(2):103-8, 2003.	No outcomes of interest
Nishiyama T. Effects of calcium on muscular training. Journal of Nutritional Science & Vitaminology 31 Suppl: S45-7, 1985.	Calcium only and bone/muscle outcomes
Nowak A, Pachocka L, Targosz U, Klosiewicz-Latoszek L. Dietary calcium and obesity in men. Roczniki Panstwowego Zakladu Higieny 58 (1):301-5, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Nowson C, Morgan T. Effect of calcium carbonate on blood pressure in normotensive and hypertensive people. Hypertension 13(6 Pt 1):630-9, 1989.	In systematic review
Obarzanek E, Hunsberger SA, Van HL et al. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). Pediatrics 100 (1):51-9, 1997.	No outcomes of interest

Excluded Study	Reason
Ochner CN, Lowe MR. Self-reported changes in dietary calcium and energy intake predict weight regain following a weight loss diet in obese women. Journal of Nutrition 2007; 137(10):2324-2328.	No outcomes of interest
Olafsdottir AS, Wagner KH, Thorsdottir I, Elmadfa I. Fat-soluble Vitamins in the maternal diet, influence of cod liver oil supplementation and impact of the maternal diet on human milk composition. Annals of Nutrition & Metabolism 45 (6):265-72, 2001.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Paganus A, Juntunen-Backman K, Savilahti E. Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatrica 81 (6-7):518 -21, 1992.	>=20% subjects with diseases
Palacios C, Benedetti P, Fonseca S. Impact of calcium intake on body mass index in Venezuelan adolescents. Puerto Rico Health Sciences Journal 26 (3):199-204, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. Pediatric Dermatology 16 (4):321-5, 1999.	No 25(OH)D or dietary Ca
Pasch A, Frey FJ, Eisenberger U, Mohaupt MG, Bonny O. PTH and 1.25 vitamin D response to a low-calcium diet is associated with bone mineral density in renal stone formers. Nephrology Dialysis Transplantation 23(8):2563 -70 , 2008.	no outcomes of interest
Pehlivan I, Hatun S, Aydogan M, Babaoglu K, Gokalp AS. Maternal Vitamin D deficiency and Vitamin D supplementation in healthy infants. Turkish Journal of Pediatrics 45 (4):315-20, 2003;-Dec.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Peters U, Hayes RB, Chatterjee N et al. Circulating Vitamin D metabolites, polymorphism in Vitamin D receptor, and colorectal adenoma risk. Cancer Epidemiology, Biomarkers & Prevention 2004; 13(4):546-552.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Peters U, McGlynn KA, Chatterjee N et al. Vitamin D, calcium, and Vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 2001; 10(12):1267-1274.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC, Ross FP. Serum levels of free 1,25-dihydroxyVitamin D in Vitamin D toxicity. Annals of Internal Medicine 122 (7):511-3, 1995.	Case report
Phillips SM, Bandini LG, Cyr H, Colclough-Douglas S, Naumova E, Must A. Dairy food consumption and body weight and fatness studied longitudinally over the adolescent period. . International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 27 (9):1106-13, 2003.	Not RCT growth study
Pilz S, Dobnig H, Fischer JE et al. Low Vitamin d levels predict stroke in patients referred to coronary angiography. Stroke 39 (9):2611-3, 2008.	>=20% subjects with diseases
Pilz S, Dobnig H, Winklhofer-Roob B et al. Low serum levels of 25-hydroxyVitamin D predict fatal cancer in patients referred to coronary angiography. Cancer Epidemiology, Biomarkers & Prevention 17(5):1228-33, 2008.	>=20% subjects with diseases
Pittard WB, III, Geddes KM, Hulsey TC, Hollis BW. How much Vitamin D for neonates? American Journal of Diseases of Children 145 (10):1147-9, 1991.	Not RCT arrow 4 study

Excluded Study	Reason
Pittard WB, III, Geddes KM, Sutherland SE, Miller MC, Hollis BW. Longitudinal changes in the bone mineral content of term and premature infants. . American Journal of Diseases of Children 1990; 144(1):36-40.	Changes in 25(OH)D status of term and premature infants
Pittas AG, Harris SS, Stark PC, wson-Hughes B. The effects of calcium and Vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults.. Diabetes Care 2007; 30(4):980-986.	No outcomes of interest
Porojnicu AC, Robsahm TE, Dahlback A et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer 2007; 55(3):263-270.	Ecological study
Prentice A, Ginty F, Stear SJ, Jones SC, Laskey MA, Cole TJ. Calcium supplementation increases stature and bone mineral mass of 16- to 18-year-old boys. Journal of Clinical Endocrinology & Metabolism 90 (6):3153-61, 2005.	In Winzenberg 2007 systematic review
Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiology 8 (1):31-6, 1997.	No outcomes of interest
Purwar M, Kulkarni H, Motghare V, Dhole S. Calcium supplementation and prevention of pregnancy induced hypertension. Journal of Obstetrics & Gynaecology Research 22 (5):425-30, 1996.	In Hofmeyer 2007 systematic review
Rajalakshmi R, Sail SS, Shah DG, Ambady SK. The effects of supplements varying in carotene and calcium content on the physical, biochemical and skeletal status of preschool children. British Journal of Nutrition 30 (1):77-86, 1973.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. American Journal of Clinical Nutrition 83 (3):559-66, 2006.	No outcomes of interest
Rees GA, Doyle W, Srivastava A, Brooke ZM, Crawford MA, Costeloe KL. The nutrient intakes of mothers of low birth weight babies - a comparison of ethnic groups in East London, UK. Maternal & Child Nutrition 1(2):91-9, 2005.	No outcomes of interest
Repke JT, Villar J, Anderson C, Pareja G, Dubin N, Belizan JM. Biochemical changes associated with blood pressure reduction induced by calcium supplementation during pregnancy. American Journal of Obstetrics & Gynecology 160 (3):684-90, 1989.	In Hofmeyer 2007 systematic review
Repke JT, Villar J. Pregnancy-induced hypertension and low birth weight: the role of calcium. American Journal of Clinical Nutrition 1991; 54(1:Suppl): Suppl-241S.	Review paper
Resnick LM, Oparil S, Chait A et al. Factors affecting blood pressure responses to diet: the Vanguard study. American Journal of Hypertension 13(9):956-65, 2000.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Reunanen A, Knekt P, Marniemi J, Maki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. European Journal of Clinical Nutrition 50 (7):431-7, 1996.	No 25(OH)D or dietary Ca
Rich GM, McCullough M, Olmedo A, Malarick C, Moore TJ. Blood pressure and renal blood flow responses to dietary calcium and sodium intake in humans. American Journal of Hypertension 4(11):642S-645S, 1991.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Roberts CC, Chan GM, Folland D, Rayburn C, Jackson R. Adequate bone mineralization in breast-fed infants. Journal of Pediatrics 99 (2):192-6, 1981.	In Ottawa EPC report
Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. Cancer Causes & Control 2007; 18(7):775-782.	Observational study estimated Vitamin D supplement doses
Rogers MS, Fung HY, Hung CY. Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension. Hypertension in Pregnancy 18 (2):165-72, 1999.	In Hofmeyer 2007 systematic review
Roongpisuthipong C, Kantawan R, Roongpisuthipong W. Reduction of adipose tissue and body weight: effect of water soluble calcium hydroxycitrate in Garcinia atroviridis on the short term treatment of obese women in Thailand. Asia Pacific Journal of Clinical Nutrition 2007; 16(1):25-29.	No 25(OH)D or dietary Ca
Rosell M, Hakansson NN, Wolk A. Association between dairy food consumption and weight change over 9 y in 19,352 perimenopausal women. American Journal of Clinical Nutrition 2006; 84(6):1481-1488.	Ca intake and BW measured but not assessed ==> no relevant results reported
Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. Maternal-infant Vitamin D relationships during breast-feeding. Journal of Pediatrics 101 (4):500-3, 1982.	In Ottawa EPC report
Rourke KM, Brehm BJ, Cassell C, Sethuraman G. Effect of weight change on bone mass in female adolescents. Journal of the American Dietetic Association 103 (3):369-72, 2003.	No 25(OH)D or dietary Ca
Rozen P, Fireman Z, Fine N, Wax Y, Ron E. Oral calcium suppresses increased rectal epithelial proliferation of persons at risk of colorectal cancer. Gut 30(5):650-5, 1989.	No outcomes of interest
Rozen P, Lubin F, Papo N et al. Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. Cancer 91 (4):833-40, 2001.	No outcomes of interest
Rumiris D, Purwosunu Y, Wibowo N, Farina A, Sekizawa A. Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. Hypertension in Pregnancy 2006; 25(3):241-253.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Rush D, Sloan NL, Leighton J et al. The National WIC Evaluation: evaluation of the Special Supplemental Food Program for Women, Infants, and Children. V. Longitudinal study of pregnant women. American Journal of Clinical Nutrition 48 (2 Suppl):439-83, 1988.	No exposure of interest
Saadi HF, Dawodu A, Afandi B et al. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Maternal & Child Nutrition 5(1):25 -32 , 2009.	arrow 4 RCT but daily doses were the same in the comparison groups (comparison of daily vs. monthly doses)
Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. Hypertension 26 (6 Pt 1):950-6, 1995.	Combinations of minerals
Sacks FM, Obarzanek E, Windhauser MM et al. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. Annals of Epidemiology 5(2):108-18, 1995.	No outcomes of interest

Excluded Study	Reason
Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. Hypertension 31 (1):131-8, 1998.	In systematic review
Saito K, Sano H, Kawahara J, Yokoyama M. Calcium supplementation attenuates an enhanced platelet function in salt-loaded mildly hypertensive patients. Hypertension 26 (1):156-63, 1995.	Data too incomplete
Sakhaee K, Baker S, Zerwekh J, Poindexter J, Garcia-Hernandez PA, Pak CY. Limited risk of kidney stone formation during long-term calcium citrate supplementation in nonstone forming subjects. Journal of Urology 152 (2 Pt 1):324-7, 1994.	No UL outcomes
Sakhaee K, Poindexter JR, Griffith CS, Pak CY. Stone forming risk of calcium citrate supplementation in healthy postmenopausal women. Journal of Urology 172 (3):958-61, 2004.	No UL outcomes: saturation of CaOx
Salazar-Martinez E, Lazcano-Ponce E, Sanchez-Zamorano LM, Gonzalez-Lira G, Escudero-DE Los RP, Hernandez-Avila M. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. International Journal of Gynecological Cancer 15 (5):938-45 , 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sampath V, Havel PJ, King JC. Calcium supplementation does not alter lipid oxidation or lipolysis in overweight/obese women. Obesity 16 (11):2400 -4, 2008.	not RCT wt study
Sanchez-Ramos L, Adair CD, Kaunitz AM, Briones DK, Del Valle GO, Delke I. Calcium supplementation in mild preeclampsia remote from term: a randomized double-blind clinical trial. Obstetrics & Gynecology 85 (6):915-8, 1995.	100% patients with already diagnosed "mild" preeclampsia
Sanchez-Ramos L, Briones DK, Kaunitz AM, Delvalle GO, Gaudier FL, Walker CD. Prevention of pregnancy-induced hypertension by calcium supplementation in angiotensin II-sensitive patients. Obstetrics & Gynecology 84 (3):349-53, 1994.	In Hofmeyer 2007 systematic review
Sanders TA, Purves R. An anthropometric and dietary assessment of the nutritional status of vegan preschool children. Journal of Human Nutrition 35 (5):349-57, 1981.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sato K, Emoto N, Toraya S et al. Progressively increased serum 1,25-dihydroxyVitamin D2 concentration in a hypoparathyroid patient with protracted hypercalcemia due to Vitamin D2 intoxication. Endocrine Journal 41 (4):329-37, 1994.	Case report
Satterfield S, Cutler JA, Langford HG et al. Trials of hypertension prevention. Phase I design. Annals of Epidemiology 1(5):455-71, 1991.	Shows research design, but no result
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.[see comment]. American Journal of Clinical Nutrition 83 (4):754 -9 , 2006.	>=20% subjects with diseases
Schumann SA, Ewigman B. Double-dose Vitamin D lowers cancer risk in women over 55. Journal of Family Practice 2007; 56(11):907-910.	Editorial-like brief review

Excluded Study	Reason
Sellers TA, Bazyk AE, Bostick RM et al. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). Cancer Causes & Control 9(4):357-67, 1998.	Same cohort as Zheng 1998 (RefID 2924) only difference is that taking into consideration the family history of colon cancer in the analysis
Shahar DR, Abel R, Elhayany A, Vardi H, Fraser D. Does dairy calcium intake enhance weight loss among overweight diabetic patients? Diabetes Care 2007; 30(3):485-489.	>=20% subjects with diseases
Shapses SA, Heshka S, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. Journal of Clinical Endocrinology & Metabolism 89 (2):632-7, 2004.	In systematic review
Sharkey JR, Giuliani C, Haines PS, Branch LG, Busby-Whitehead J, Zohoori N. Summary measure of dietary musculoskeletal nutrient (calcium, Vitamin D, magnesium, and phosphorus) intakes is associated with lower-extremity physical performance in homebound elderly men and women. American Journal of Clinical Nutrition 77 (4):847-56, 2003.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Shaunak S, Ang L, Colston K, Patel S, Bland M, Maxwell JD. Muscle strength in healthy white and Asian subjects: the relationship of quadriceps maximum voluntary contraction to age, sex, body build and Vitamin D. Clinical Science 73 (5):541-6, 1987.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sibai BM, Ewell M, Levine RJ et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. . American Journal of Obstetrics & Gynecology 177 (5):1003-10, 1997.	No Ca dose
Sieg J, Sieg A, Dreyhaupt J, Schmidt-Gayk H. Insufficient Vitamin D supply as a possible co-factor in colorectal carcinogenesis. Anticancer Research 26 (4A):2729 -33, 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Silverman SL, Delmas PD, Kulkarni PM, Stock JL, Wong M, Plouffe L, Jr. Comparison of fracture, cardiovascular event, and breast cancer rates at 3 years in postmenopausal women with osteoporosis. Journal of the American Geriatrics Society 52 (9):1543-8, 2004.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Sita-Lumsden A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and Vitamin D deficiency: the contribution of diet and exposure to sunlight. Thorax 62 (11):1003-7, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Siwek RA, Burkinshaw L, Oxby CB, Robinson PA. Multi-element analysis of the obese subject by in vivo neutron activation analysis. Physics in Medicine & Biology 29 (6):687-701, 1984.	Not relevant
Skinner JD, Bounds W, Carruth BR, Ziegler P. Longitudinal calcium intake is negatively related to children's body fat indexes.. Journal of the American Dietetic Association 103 (12):1626-31, 2003.	Not RCT growth study
Slemenda CW, Reister TK, Hui SL, Miller JZ, Christian JC, Johnston CC, Jr. Influences on skeletal mineralization in children and adolescents: evidence for varying effects of sexual maturation and physical actiVitaminy. Journal of Pediatrics 125 (2):201-7, 1994.	No 25(OH)D or dietary Ca
Specker BL, Beck A, Kalkwarf H, Ho M. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. Pediatrics 99(6): E12, 1997.	No independent Ca effect

Excluded Study	Reason
Specker BL, Tsang RC, Ho M, Miller D. Effect of vegetarian diet on serum 1,25-dihydroxyVitamin D concentrations during lactation. Obstetrics & Gynecology 70 (6):870-4, 1987.	No 25(OH)D or dietary Ca
Specker BL, Valanis B, Hertzberg V, Edwards N, Tsang RC. Sunshine exposure and serum 25-hydroxyVitamin D concentrations in exclusively breast-fed infants. Journal of Pediatrics 107 (3):372-6, 1985.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension 39 (5):1000-6, 2002.	No outcomes of interest
Stern HS, Gregoire RC, Kashtan H, Stadler J, Bruce RW. Long-term effects of dietary calcium on risk markers for colon cancer in patients with familial polyposis. Surgery 108 (3):528-33, 1990.	No outcomes of interest
Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabetic Medicine 2008;25:320-5.	>=20% subjects with diseases
Swanenburg J, de Bruin ED, Stauffacher M, Mulder T, Uebelhart D. Effects of exercise and nutrition on postural balance and risk of falling in elderly people with decreased bone mineral density: randomized controlled trial pilot study. Clinical Rehabilitation 2007; 21(6):523-534.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Takeuchi A, Okano T, Tsugawa N et al. Effects of ergocalciferol supplementation on the concentration of Vitamin D and its metabolites in human milk. Journal of Nutrition 119 (11):1639-46, 1989.	Not RCT arrow 4 study
Tanji JL, Lew EY, Wong GY, Treguboff C, Ward JA, Amsterdam EA. Dietary calcium supplementation as a treatment for mild hypertension.. Journal of the American Board of Family Practice 4(3):145-50, 1991.	In systematic review
Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. Journal of the American Society of Nephrology 15 (12):3225-32, 2004.	No outcomes of interest
Teegarden D, White KM, Lyle RM et al. Calcium and dairy product modulation of lipid utilization and energy expenditure. Obesity 16 (7):1566-72, 2008.	No outcomes of interest
Thompson IM, Coltman CA, Jr., Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. Prostate 33 (3):217-21, 1997.	Commentary
Thompson WG, Rostad HN, Janzow DJ, Slezak JM, Morris KL, Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. . Obesity Research 13(8):1344-53, 2005.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Thomson K, Morley R, Grover SR, Zacharin MR. Postnatal evaluation of Vitamin D and bone health in women who were Vitamin D-deficient in pregnancy, and in their infants.[erratum appears in Med J Aust. 2005 Jan 3;182(1):48 Note: Thompson, Katherine [corrected to Thomson, Katherine]]. Medical Journal of Australia 181 (9):486-8, 2004.	No analysis of association between 25(OH)D and outcomes
Tomoda S, Kitanaka T, Ogita S, Hidaka A. Prevention of pregnancy-induced hypertension by calcium dietary supplement: a preliminary report. Journal of Obstetrics & Gynaecology 21(3):281-8, 1995.	No outcomes of interest

Excluded Study	Reason
Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. British Journal of Cancer 100 (3):450 -4, 2009.	>=20% subjects with diseases
Tsang RC, Gigger M, Oh W, Brown DR. Studies in calcium metabolism in infants with intrauterine growth retardation. Journal of Pediatrics 86 (6):936-41, 1975.	No 25(OH)D or dietary Ca
Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyVitamin D and 1,25-dihydroxyVitamin D and risk of incident ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention 2007; 16(4):783-788.	No outcomes of interest
van Beresteijn EC, Riedstra M, van der WA, Schouten EG, Burema J, Kok FJ. Habitual dietary calcium intake and blood pressure change around the menopause: a longitudinal study. International Journal of Epidemiology 21(4):683-9, 1992.	No outcomes of interest
van Buul BJ, Steegers EA, Jongsma HW et al. Dietary sodium restriction in the prophylaxis of hypertensive disorders of pregnancy: effects on the intake of other nutrients. American Journal of Clinical Nutrition 62 (1):49-57, 1995.	Ca intake and BM (mothers and neonates) measured but not assessed ==> no relevant results reported
Vatanparast H, Baxter-Jones A, Faulkner RA, Bailey DA, Whiting SJ. Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. American Journal of Clinical Nutrition 82 (3):700-6, 2005.	No 25(OH)D or dietary Ca
Vergnaud AC, Peneau S, Chat-Yung S et al. Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. American Journal of Clinical Nutrition 88 (5):1248 -55 , 2008.	not RCT (weight outcome)
Verhaar HJ, Samson MM, Jansen PA, de Vreede PL, Manten JW, Duursma SA. Muscle strength, functional mobility and Vitamin D in older women.. Aging-Clinical & Experimental Research 12 (6):455-60, 2000.	In Ottawa EPC report
Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum Vitamin d does not predict new disability or loss of muscle strength in older women. . Journal of the American Geriatrics Society 50 (5):912-7, 2002.	In Ottawa EPC report
Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum Vitamin d does not predict new disability or loss of muscle strength in older women. . Journal of the American Geriatrics Society 50(5):912-7, 2002.	In Ottawa EPC report
Villar J, bdel-Aleem H, Merialdi M et al. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. American Journal of Obstetrics & Gynecology. 194(3):639-49, 2006 Mar.	In Hofmeyer 2007 systematic review, systematic review
Villar J, Gulmezoglu AM, de OM. Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomized controlled trials. Obstetrical & Gynecological Survey 53 (9):575-85 , 1998 Sep.	Not relevant systematic review

Excluded Study	Reason
Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. American Journal of Obstetrics & Gynecology 163 (4 Pt 1):1124 -31, 1990.	In Hofmeyer 2007 systematic review
Visser M, Deeg DJ, Lips P, Longitudinal Aging SA. Low Vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. Journal of Clinical Endocrinology & Metabolism 88 (12):5766-72, 2003.	In Ottawa EPC report
von Hurst PR, Stonehouse W, Matthys C, Conlon C, Kruger MC, Coad J. Study protocol--metabolic syndrome, vitamin D and bone status in South Asian women living in Auckland, New Zealand: a randomised, placebo-controlled, double-blind vitamin D intervention. BMC Public Health 8 :267 , 2008.	RCT protocol only
Wallace K, Baron JA, Cole BF et al. Effect of calcium supplementation on the risk of large bowel polyps.[see comment]. Journal of the National Cancer Institute 96 (12):921 -5, 2004.	In Weigarten 2008 SR
Wallace K, Baron JA, Karagas MR et al. The association of physical actiVitaminy and body mass index with the risk of large bowel polyps. Cancer Epidemiology, Biomarkers & Prevention 14(9):2082-6, 2005.	No outcomes of interest
Waltman NL, Twiss JJ, Ott CD et al. Testing an intervention for preventing osteoporosis in postmenopausal breast cancer survivors. Journal of Nursing Scholarship 35 (4):333-8, 2003.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Wanchu M, Malhotra S, Khullar M. Calcium supplementation in pre-eclampsia. Journal of the Association of Physicians of India 49:795-8, 2001.	In Hofmeyer 2007 systematic review
Wang LD, Qiu SL, Yang GR, Lipkin M, Newmark HL, Yang CS. A randomized double-blind intervention study on the effect of calcium supplementation on esophageal precancerous lesions in a high-risk population in China. Cancer Epidemiology, Biomarkers & Prevention 2(1):71-8, 1993.	>=20% subjects with diseases
Wargovich MJ, Isbell G, Shabot M et al. Calcium supplementation decreases rectal epithelial cell proliferation in subjects with sporadic adenoma. . Gastroenterology 103 (1):92-7, 1992.	No outcomes of interest
Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyVitamin D in an elderly nursing home population in Boston. American Journal of Clinical Nutrition 51 (6):1075-81, 1990.	Not RCT arrow 4 study
Webber CE, Blake JM, Chambers LF, Roberts JG. Effects of 2 years of hormone replacement upon bone mass, serum lipids and lipoproteins. Maturitas. 19(1):13-23, 1994 May.	No 25(OH)D or dietary Ca
Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. Journal of the National Cancer Institute 97 (22):1688-94, 2005.	No 25(OH)D or dietary Ca

Excluded Study	Reason
Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. American Journal of Hypertension 6 (9):799-805, 1993.	In systematic review
Weisgerber UM, Boeing H, Owen RW, Waldherr R, Raedsch R, Wahrendorf J. Effect of longterm placebo controlled calcium supplementation on sigmoidal cell proliferation in patients with sporadic adenomatous polyps. Gut 38 (3):396-402, 1996.	No outcomes of interest
Weisman Y, Bawnik JC, Eisenberg Z, Spirer Z. Vitamin D metabolites in human milk. Journal of Pediatrics 100 (5):745-8, 1982.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Weston TL, Aronson KJ, Siemiatycki J, Howe GR, Nadon L. Cancer mortality among males in relation to exposures assessed through a job-exposure matrix. International Journal of Occupational & Environmental Health 6(3):194-202, 2000.	No 25(OH)D or dietary Ca
Widga AC, Lewis NM. Defined, in-home, prenatal nutrition intervention for low-income women. Journal of the American Dietetic Association 99(9):1058-62, 1999.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990; 323(24):1664-1672.	No 25(OH)D or dietary Ca
Williams CP, Child DF, Hudson PR et al. Why oral calcium supplements may reduce renal stone disease: report of a clinical pilot study. Journal of Clinical Pathology 54 (1):54-62, 2001.	No UL outcomes
Wimalawansa SJ. Antihypertensive effects of oral calcium supplementation may be mediated through the potent vasodilator CGRP. American Journal of Hypertension 6 (12):996-1002, 1993.	n=8, Ca to Rx HTN
Witteman JC, Willett WC, Stampfer MJ et al. A prospective study of nutritional factors and hypertension among US women. Circulation 80 (5):1320-7, 1989.	Superceded by Ascherio (4022)
Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of Vitamin D in obesity. [erratum appears in Am J Clin Nutr. 2003 May;77(5):1342]. American Journal of Clinical Nutrition 72 (3):690-3, 2000.	Not RCT arrow 4 study
Wosje KS, Kalkwarf HJ. Lactation, weaning, and calcium supplementation: effects on body composition in postpartum women. American Journal of Clinical Nutrition 80 (2):423-9, 2004.	No outcomes of interest
Wyatt HR, Jortberg BT, Babbel C et al. Weight loss in a community initiative that promotes decreased energy intake and increased physical actiVitaminy and dairy consumption: Calcium Weighs-In. Journal of Physical ActiVitaminy & Health 5(1):28-44, 2008.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Yang YX, Han JH, Shao XP et al. Effect of micronutrient supplementation on the growth of preschool children in China. Biomedical & Environmental Sciences 15 (3):196-202, 2002.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Yesudian PD, Berry JL, Wiles S et al. The effect of ultraviolet B-induced Vitamin D levels on host resistance to Mycobacterium tuberculosis: a pilot study in immigrant Asian adults living in the United Kingdom. Photodermatology, Photoimmunology & Photomedicine 24 (2):97-8, 2008.	No outcomes of interest
Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obesity Research 13(7):1218 -25, 2005.	In systematic review
Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. . Obesity Research 12 (4):582-90, 2004.	In systematic review
Zhang Y, Kiel DP, Ellison RC et al. Bone mass and the risk of prostate cancer: the Framingham Study. American Journal of Medicine 113 (9):734 -9, 2002.	No 25(OH)D or dietary Ca
Zhou C, Fan S, Zhou L, Ni Y, Huang T, Shi Y. Clinical observation of treatment of hypertension with calcium. American Journal of Hypertension 7 (4 Pt 1):363-7, 1994.	In systematic review
Zofkova I, Hill M. Long-term 1,25(OH)2 Vitamin D therapy increases bone mineral density in osteopenic women. Comparison with the effect of plain Vitamin D. Aging-Clinical & Experimental Research. 19(6):472-7, 2007 Dec.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Zorbas YG, Petrov KL, Kakurin VJ et al. Calcium supplementation effect on calcium balance in endurance-trained athletes during prolonged hypokinesia and ambulatory conditions. Biological Trace Element Research 73 (3):231-50, 2000.	Arrow 4: calcium balance