



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



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

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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 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 and strategies. 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 and public comment prior to their release as a final report.

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.hhs.gov.

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

Structured Abstract

Background. In 2009, the Institute of Medicine/Food and Nutrition Board constituted a Dietary Reference Intakes (DRI) committee to undertake a review of the evidence that had emerged (since the 1997 DRI report) on the relationship of vitamin D and calcium, both individually and combined, to a wide range of health outcomes, and potential revision of the DRI values for these nutrients. To support that review, several United States and Canadian Federal Government agencies commissioned a systematic review of the scientific literature for use during the deliberations by the committee. The intent was to support a transparent literature review process and provide a foundation for subsequent reviews of the nutrients. The committee used the resulting literature review in their revision of the DRIs.

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decisionmaking for vitamin D in primary care, based on the updated DRI report, the ODS and AHRQ requested an update to the 2009 systematic review to incorporate the findings of studies conducted since the 2009 evidence review on the relationship between vitamin D alone or vitamin D plus calcium to selected health outcomes and to report on the methods used to assay vitamin D in the included trials.

Purpose. To systematically summarize the evidence on the relationship between vitamin D alone or in combination with calcium on selected health outcomes included in the earlier review: primarily those related to bone health, cardiovascular health, cancer, immune function, pregnancy, all-cause mortality, and vitamin D status; and to identify the vitamin D assay methods and procedures used for the interventional studies that aimed to assess the effect of vitamin D administration on serum 25(OH)D concentrations, and to stratify key outcomes by methods used to assay serum 25(OH)D concentrations.

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

Study selection. Primary interventional or prospective observational studies that reported outcomes of interest in human subjects in relation to vitamin D alone or in combination with calcium, as well as systematic reviews that met the inclusion and exclusion criteria.

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 154 newly identified primary articles and two new systematic reviews that incorporated more than 93 additional primary articles. Available evidence focused mainly on bone health, cardiovascular diseases, or cancer outcomes. Findings were inconsistent across studies for bone health; breast, colorectal, and prostate cancer; cardiovascular disease and mortality; immune function; and pregnancy-related outcomes. Few studies assessed pancreatic cancer and birth outcomes. One new systematic review of observational studies found that

circulating 25(OH)D was generally inversely associated with risk for cardiovascular disease. Methods used to assay serum 25(OH)D in studies reporting on key outcomes diverged widely. The current report also identified one new systematic review published since the original report that addressed whether a dose response relationship exists between dietary and supplemental vitamin D intake and serum 25(OH)D concentrations. The systematic review, based on 76 RCTs, reported widely varying increases in serum concentrations of 25(OH)D for similar doses of vitamin D, with a general increase in serum concentration with dietary intake. The RCTs identified for the current report found increases in serum 25(OH)D with supplementation; however, the findings varied by age group and health status of participants, baseline vitamin D status, dose, duration, and assay used to assess serum 25(OH)D.

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 and were often underpowered for their intended outcomes. Studies vary widely in methodological quality and in the assays used to measure vitamin D status.

Conclusions. In solid agreement with the findings of the original report, the majority of the findings concerning vitamin D, alone or in combination with calcium, on the health outcomes of interest were inconsistent. Associations observed in prospective cohort and nested case-control studies were inconsistent, or when consistent, were rarely supported by the results of randomized controlled trials. Clear dose-response relationships between intakes of vitamin D and health outcomes were rarely observed. Although a large number of new studies (and longer followups to older studies) were identified, particularly for cardiovascular outcomes, all-cause mortality, several types of cancer, and intermediate outcomes for bone health, no firm conclusions can be drawn. Studies identified for the current report suggest a possible U-shaped association between serum 25(OH)D concentrations and both all-cause mortality and hypertension and also suggest that the level of supplemental vitamin D and calcium administered in the Women's Health Initiative Calcium-Vitamin D Trial are not associated with an increased risk for cardiovascular disease or cancer among postmenopausal women who are not taking additional supplemental vitamin D and calcium. Studies suggest the method used to assay 25(OH)D may influence the outcomes of dose-response assessments. Beyond these observations, 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.

Contents

Executive Summary	ES-1
Introduction	1
Background	1
Sources, Metabolism and Functions of Vitamin D	2
Sources, Metabolism, and Functions of Calcium	5
Challenges for the DRI Committees	5
Key Questions Addressed in This Report	7
Methods	9
Overview	9
Sponsoring Federal Agencies	9
AHRQ Task Order Officer	9
Technical Expert Panel	9
EPC Methodologists	10
Development of the Analytic Framework and Refinement of Key Questions	10
Definitions	12
Vitamin D and Calcium Exposures	12
Clinical Outcomes	13
Indicators of Exposure (Nutrient Intake)	13
Surrogate Outcomes	13
Intermediate Outcomes	13
Life Stages	13
Key Questions	14
Literature Search Strategy	15
Study Selection	16
Abstract Screening	16
Full-Text Article Eligibility Criteria	16
Other Specific Eligibility Criteria	19
Data Extraction	20
Data Analysis	21
MetaAnalysis	22
Grading of Studies Analyzed in This Evidence Report	22
Critical Appraisal and Grading of Primary Studies	22
Grade A	23
Grade B	23
Grade C	23
Additional Considerations of Methodological Quality of Primary Studies for the Purpose of DRI Decisionmaking	24
Critical Appraisal of Systematic Reviews	24
Reporting of the Evidence	25
Evidence Tables	25
Summary Tables	25
Graphical Presentation of Dose-Response Relationship	25
Grand Summary Tables (Evidence Map)	25
Units of Measurement	26
Assay Method	26

Sunlight Exposure.....	26
Primary and Secondary Outcomes.....	27
Study Quality	27
Peer Review and Public Commentary	27
Results	28
Organization of the Results Section.....	28
Literature Search Results	28
Vitamin D and Health Outcomes	33
Vitamin D and Growth.....	33
Vitamin D and Cardiovascular Disease	48
Vitamin D and Body Weight	89
Vitamin D and Cancer	93
Vitamin D and Immunologic Outcomes	163
Vitamin D and Pregnancy-Related Outcomes	187
Vitamin D and Clinical Outcomes of Bone Health	199
Vitamin D and All-Cause Mortality	224
Vitamin D and Hypertension and Blood Pressure	242
Vitamin D and Bone Mineral Density or Bone Mineral Content	260
Combined Vitamin D and Calcium and Health Outcomes	273
Combined Vitamin D and Calcium and Growth.....	273
Combined Vitamin D and Calcium and Cardiovascular Disease	274
Combined Vitamin D and Calcium and Body Weight	280
Combined Vitamin D and Calcium and Cancer	284
Combined Vitamin D and Calcium and Pregnancy-Related Outcomes	295
Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health	298
Combined Vitamin D and Calcium and All-Cause Mortality	306
Combined Vitamin D and Calcium and Hypertension and Blood Pressure	310
Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content.....	317
How Does Dietary Intake of Vitamin D From Fortified Foods and Vitamin D Supplementation Affect Serum 25(OH)D Concentrations (Arrow 4)?	328
RCTs on Dietary Intakes of Vitamin D From Fortified Foods and Serum 25(OH)D Concentrations	328
RCTs on Vitamin D Supplementation and Serum 25(OH)D Concentrations	329
Stratification of Key Outcomes by Vitamin D Assay Method	339
Outcomes for Tolerable Upper Intake Levels.....	339
Renal Outcomes	339
Adverse Events Reported in RCTs	340
Discussion	346
Strengths of This Report	347
DRI and the Literature on Vitamin D and Calcium	348
Limitations of Our Methodological Approach	349
Comments on the Observational Studies	350
Sources of Heterogeneity and Potential Biases	351
Vitamin D Intake and Response in Serum 25(OH)D Concentration	351
Considerations for Future DRI Committees	352

References	353
Abbreviations	371
Latitudes of Selected Cities	374

Tables

Table A. Findings of the original report compared with the current report.....	ES-21
Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages [updated for the current report].....	31
Table 2. Number of primary studies on calcium intake and specific health outcomes that could be applicable to certain life stages [not updated in the current report]	32
Table 3. Number of primary studies on combined vitamin D and calcium intake and specific health outcomes that are relevant to certain life stages [updated for the current report].....	33
Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report)	38
Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)	41
Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report)	42
Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report).....	45
Table 8. Vitamin D and cardiovascular outcomes: Characteristics of RCTs [no new studies in the current report]	54
Table 9. Vitamin D and cardiovascular outcomes: Results of RCTs [no new studies in the current report]	55
Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report)	56
Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report)	65
Table 11b. Vitamin D and cardiovascular outcomes: Results of nested case-control studies (new table)	80
Table 12. Vitamin D and weight: Characteristics of RCTs [no new studies in the current report].....	91
Table 13. Vitamin D and weight: Results of RCTs [no new studies in the current report].....	92
Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report]	96
Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report)	97
Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report]	100
Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report)	101
Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)	110
Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report)	115
Table 20. Vitamin D and colorectal cancer: Characteristics of RCTs [no new studies in the current report]	123

Table 21. Vitamin D and colorectal cancer: Results of RCTs [no new studies in the current report].....	124
Table 22. Vitamin D and colorectal cancer: Characteristics of observational studiesA (updated from original report)	128
Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report)	132
Table 24. Vitamin D and colorectal adenoma: Characteristics of observational studies [no new studies in the current report]	143
Table 25. Vitamin D and colorectal adenoma: Results of observational studies [no new studies in the current report]	144
Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report)	148
Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report)	150
Table 26c. Vitamin D and breast density: Characteristics of RCTs (updated from original report).....	151
Table 26d Vitamin D and breast density: Characteristics of nested case-control studies (updated from original report)	151
Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report)	152
Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report)	155
Table 27c. Vitamin D and breast density: Results of RCTs (updated from original report)	156
Table 27d. Vitamin D and breast density: Results of nested case-control studies (updated from original report)	157
Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies (updated from original report)	160
Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report)	161
Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report).....	169
Table 30b. Vitamin D and immunologic outcomes: Characteristics of autoimmune disease RCTs (updated from original report)	176
Table 30c. Vitamin D and immunologic outcomes: Characteristics of infectious disease continuous RCTs (updated from original report).....	176
Table 30d. Vitamin D and immunologic outcomes: Characteristics of infectious disease dichotomous RCTs (updated from original report)	177
Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report).....	178
Table 31b. Vitamin D and immunologic outcomes: Results of autoimmune disease RCTs (updated from original report)	184
Table 31c. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (continuous outcomes) (updated from original report).....	184
Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report).....	185

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report)	191
Table 32b. Vitamin D and other pregnancy outcomes: Characteristics of observational studies (updated from original report)	193
Table 32c. Vitamin D and preeclampsia: Characteristics of RCTs (updated from original report).....	194
Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report)	195
Table 33b. Vitamin D and other pregnancy outcomes: Results of observational studies (updated from original report)	197
Table 33c. Vitamin D and preeclampsia: results of RCTs (updated from original report)	198
Table 34. Summary of systematic review of the effect of vitamin D on bone health (not updated from original report)	201
Table 35a. Vitamin D and bone health: Characteristics of RCTs published after the Ottawa EPC report (updated from original report).....	206
Table 35b. Vitamin D and muscle strength: Characteristics of RCTs (updated from original report).....	207
Table 35c. Vitamin D and muscle strength: Characteristics of prospective cohorts (updated from original report)	208
Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report).....	209
Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original report).....	212
Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report).....	214
Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report)	217
Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report).....	221
Table 37. Summary of systematic review on vitamin D supplementation and all-cause mortality (not updated from original report).....	225
Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report)	228
Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report)	233
Table 40. Vitamin D and hypertension: Characteristics of cohort studies (updated from original report)	245
Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report)	246
Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report).....	251
Table 43. Vitamin D and blood pressure: Results of RCTs.....	255
Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report).....	264
Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report)	267

Table 46. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs (formerly Table 85) (updated from original report)	277
Table 47. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs (formerly Table 86) (updated from original report).....	278
Table 48. Combined vitamin D and calcium and weight: Characteristics of RCTs (formerly Table 87) (no new studies in the current report).....	282
Table 49. Combined vitamin D and calcium and weight: Results of RCTs (formerly Table 88) [no new studies in the current report]	283
Table 50. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs (formerly Table 89) (updated from original report)	285
Table 51. Combined vitamin D and calcium and total cancer incidence: Results of RCTs (formerly Table 90) (updated from original report).....	286
Table 52. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs (formerly Table 91) [no new studies in the current report].....	289
Table 53. Combined vitamin D with calcium and colorectal cancer: Results of RCTs (formerly Table 92) [no new studies in the current report]	290
Table 54. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs (formerly Table 93) [no new studies in the current report].....	293
Table 55. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs (formerly Table 94) [no new studies in the current report]	294
Table 56. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs (formerly Table 95) [no new studies in the current report]	296
Table 57. Combined vitamin D and calcium and preeclampsia: Results of RCTs (formerly Table 96) [no new studies in the current report].....	297
Table 58. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 97) (updated from original report)	301
Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report).....	302
Table 60. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures) (formerly Table 99) (updated from original report)	305
Table 61. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs [no new studies in the current report].....	311
Table 62. Combined vitamin D and calcium and incident hypertension: Results of RCTs [no new studies in the current report]	312
Table 63. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs (formerly Table 102) [no new studies in the current report]	315
Table 64. Combined vitamin D and calcium and blood pressure: Results of RCTs (formerly Table 103) [no new studies in the current report].....	316
Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) (no new studies in the current report).....	320
Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) (no new studies in the current report)	322

Table 67. The relationship between vitamin D3 daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report).....	336
Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report).....	342

Figures

Figure 1. Summary of the vitamin D endocrine system [updated figure for the current report]	4
Figure 2. Generic analytic framework to assist formulation of Key Questions for the development of DRIs.	8
Figure 3. Analytic framework for vitamin D with or without calcium: EARs [revised for the current report]	11
Figure 4. Analytic framework for vitamin D with or without calcium ULs [revised for the current report]	12
Figure 5a. Literature flow for the original report.....	29
Figure 5b. Literature flow for the current report.....	30
Figure 6a. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes	81
Figure 6b. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes by gender	82
Figure 6c. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality.....	83
Figure 6d. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality by gender	84
Figure 6e. Cardiovascular outcomes risk stratified by vitamin D concentration for myocardial infarction	85
Figure 6g. Cardiovascular outcomes risk stratified by vitamin D concentration for fatal stroke	87
Figure 6h. Cardiovascular outcomes risk stratified by vitamin D concentration for congestive heart failure	88
Figure 7. Prostate cancer risk stratified by vitamin D concentration (updated from original report)	121
Figure 8. Colorectal cancer risk stratified by vitamin D concentration	139
Figure 9. Colon cancer risk stratified by vitamin D concentration.....	140
Figure 10. Rectal cancer risk stratified by vitamin D concentration	141
Figure 11. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality (formerly Figure 22)	309
Figure 12. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs (formerly Figure 23)	332
Figure 13. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults (formerly Figure 24)	333
Figure 14. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults (formerly Figure 25)	334
Figure 15. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by assay type (new figure)	335

Appendixes

Appendix A. Search Strategy for Primary Studies

Appendix B. Search Strategy for Systematic Reviews

Appendix C. Evidence Tables for the Current Report

Appendix D. Evaluation of Existing Systematic Reviews and Evidence Tables of the Qualified Systematic Reviews

Appendix E. Blank Data Extraction Form and Quality Assessment Checklists

Appendix F. Excluded Studies

Appendix G. Serum Vitamin D Assay Reporting in Randomized Controlled Trials (RCTs)

Appendix H. Studies Reporting Key Outcomes Stratified by Vitamin D Assay Method

Executive Summary

Background

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

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

In May and September 2007, two conferences were held on the effect of vitamin D on health. Subsequently, a working group of scientists from the United States and Canadian Governments convened to determine whether enough new research had been published since the 1997 vitamin D DRI to justify an update. Upon reviewing the conference proceedings and results from a recent systematic review, the group concluded that sufficient new data beyond bone health had been published. Areas of possible relevance included new data on bone health for several of the life stage groups, reports on potential adverse effects, dose-response relations between intakes and circulating 25-hydroxyvitamin D (25(OH)D) concentrations and between 25(OH)D concentrations, and several health outcomes.

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

This update was requested by the sponsor in anticipation of a conference focused on the evaluation of evidence related to vitamin D and health outcomes, but the update can also be helpful to other stakeholders. The sponsor's interest was to determine whether the inclusion of newer relevant data that became available during the period following the close of the 2009 review would alter or continue to support the conclusions of the 2009

report. The sponsor’s interest did not include the topic area of calcium alone or of growth and body weight as they relate to vitamin D, so for reasons of cost these components of the original report were not included in this review.

The **original** report included a systematic review of health outcomes relating to vitamin D and calcium intakes, both alone and in combination; **the current report updates that systematic review for outcomes relating to intakes of vitamin D alone or in combination with calcium.** The executive summary provides a high-level overview of the findings of the systematic review; **the summary of studies included in the current report is in boldface type.** Recommendations and potential revisions of nutrient reference values (i.e., the new DRIs) based on this review are the responsibility of the IOM committee and are beyond the scope of this report.

Methods

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

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

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

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

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

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

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

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

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

Results

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

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

Vitamin D

Vitamin D and Growth

For the current report, we identified five new RCTs (reported in four articles) and two new observational studies that evaluated intake of or exposure to vitamin D, respectively, on birth weight and/or length. In the current report, five RCTs (reported in four articles) reported on the effect of vitamin D supplementation during pregnancy on birth weight and/or length. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400 international units (IU) vitamin D per day at 16 weeks gestation

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

As reviewed in the original report, six RCTs, one nonrandomized comparative intervention study, and two observational studies evaluated intake of vitamin D or serum 25(OH)D concentrations and growth parameters in infants and children. The studies had diverse populations and methodological approaches. One RCT and one observational study were rated B; seven studies were rated C. Most studies found no significant associations between either maternal or offspring vitamin D intake and offspring's weight or height, but two C-rated intervention studies from the same center in India found a significant effect of total maternal vitamin D intake of 1.2 million IU and increased infant birth weights.

Vitamin D and Cardiovascular Events

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

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

associations between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke.

Vitamin D and Body Weight

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

Vitamin D and Cancer

Cancer From All Causes

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

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

Prostate Cancer

In the current report, four new nested case-control studies (two rated A, two rated B) and one new prospective cohort study (rated B) found no association between baseline serum 25(OH)D concentrations and risk for prostate cancer. Two new nested case-control studies (both rated B) observed a trend between higher serum vitamin D concentrations and increasing risk for prostate cancer. In one study this increase was seen only among men whose sera were sampled in summer or autumn; in the other study, this trend was observed only when participants were divided by quartiles of 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency (concentrations less than 50 nmol/L being considered deficient, 50–75 nmol/L insufficient, and 75–125 nmol/L considered sufficient).

In the original report, 12 nested case-control studies (3 rated B, 9 C) evaluated the association of baseline serum 25(OH)D concentrations and prostate cancer risk. No eligible

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

Colorectal Cancer

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

The original report identified one B-rated RCT, one B-rated cohort study, and seven nested case-control studies (five rated B, two C) that evaluated the association between vitamin D exposure and colorectal cancer. The RCT of elderly population reported no significant difference in colorectal cancer incidence or mortality with or without vitamin D₃ supplements over 5 years of followup. Most nested case-control studies found no significant associations between serum 25(OH)D concentrations and risk of colorectal cancer incidence or mortality. However, two of the three B-rated nested case-control studies in women found statistically significant trends between higher serum 25(OH)D concentrations and lower risk of colorectal cancer, but no individual quantile of serum 25(OH)D concentration had a significantly increased risk of colorectal cancer (compared with the reference quantile). The B-rated cohort study of women also suggested an association between higher serum 25(OH)D concentrations (>50 nmol/L) and lower risk of colorectal cancer mortality. The studies of men or of both sexes, and of specific cancers, did not have consistent findings of associations.

Colorectal Polyps

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

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

Breast Cancer

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

studies found increasing risk of breast cancer with decreasing 25(OH) concentrations (both rated B).

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

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

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

Pancreatic Cancer

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

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

Vitamin D and Immunologic Outcomes

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

association” refers to an association between higher serum 25(OH)D concentration and a higher risk for the outcome.) A study of healthy U.S. adults found an association between serum concentrations of 25(OH)D levels of 95 nmol/L or higher and reduced risk for acute respiratory viral infections (rated B). One study of adults observed an inverse association of serum 25(OH)D with risk for respiratory disease mortality, and another observed an inverse association with risk for pneumonia (both rated B).

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

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

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

Vitamin D and Pregnancy-Related Outcomes

Preeclampsia

For the current report, we identified one article that reported on two combined RCTs assessing the effect of supplemental vitamin D on the risk for preeclampsia: Supplementation with 4,000 IU per day decreased the risk for preeclampsia. We also identified five new nested case-control studies and two prospective cohort studies (all rated B), of which three of the nested case-control studies and the two prospective case-control

studies observed an association between 25(OH)D concentrations less than 50 nmol/L and preeclampsia or severe preeclampsia. The other two nested case-control studies (the Canadian EMMA study and a U.S. study) observed no association between low first trimester maternal 25(OH)D levels and severe preeclampsia.

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

Other Outcomes

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

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

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

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

Vitamin D and Bone Health

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

Rickets

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

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

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

Fractures, Falls, or Performance Measures of Strength

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

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

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

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

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

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

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

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

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

Bone Mineral Density or Bone Mineral Content

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

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

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

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

Vitamin D and All-Cause Mortality

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

The assessment of the literature on vitamin D and all-cause mortality in the original report was based on a reanalysis of an existing systematic review and metaanalysis of RCTs on vitamin D supplementation for mortality. One additional C-rated RCT was identified. Four additional cohort studies (one rated B, three C) on the association of vitamin D and all-cause mortality also qualified. Four RCTs (N=13,899) were included in the reanalysis of the systematic review. In each study, mean age was older than 70 years and dosages ranged between 400 to 880 IU per day. Vitamin D supplementation had no significant effect on all-cause mortality (summary relative risk [RR]=0.97, 95% CI 0.92, 1.02; random effects model). There is little evidence for between-study heterogeneity in these analyses. Three of the cohort studies found no significant association between 25(OH)D concentrations and all-cause mortality, but one found a significant trend for lower odds of death with increasing 25(OH)D concentrations, greater than 23 nmol/L in men and greater than 19 nmol/L in women.

Vitamin D and Hypertension and Blood Pressure

Hypertension

For the current report we identified no new RCTs that addressed the relationship of serum 25(OH)D concentrations or supplementation with hypertension. A large prospective cohort study identified for the current report that evaluated the association between serum 25(OH)D concentration and the risk for hypertension using the Intermountain database found a highly significant association of very low and low baseline serum 25(OH)D concentrations and the prevalence of hypertension at an average of 1.3 years followup (rated C). The Intermountain data were analyzed with 25(OH)D cutoff points of 37.5 and 75 nmol/L. Significant associations were identified for those with serum concentrations

below 75 nmol/L. An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians' Health Study (men of average age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile (rated A).

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

Blood Pressure

The current study identified 10 new RCTs that assessed the effects of 1 or more dosage levels of vitamin D compared with placebo on blood pressure in adults. Dosages ranged from 125 IU to 5700 IU per day. Followup ranged from 3 months to 1 year. Participants included postmenopausal women; middle-aged U.S. blacks (rated A); overweight young Chinese and Dutch adults; healthy South Asian women residing in the United Kingdom; and healthy young women from Spain. Of the 10 RCTs, no effect of vitamin D supplementation was observed in 7 (5 rated A and 2 rated B); vitamin D significantly decreased systolic blood pressure in 2 studies (both systolic and diastolic in one of the studies) (rated B); and in the final study, systolic blood pressure actually increased slightly in the supplemented group (rated C).

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

Combined Vitamin D and Calcium

Combined Vitamin D and Calcium and Growth

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

Combined Vitamin D and Calcium and Cardiovascular Events

For the original study, a variety of cardiovascular events after 7 years were evaluated in the WHI trial of combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) (CaD) versus placebo in postmenopausal women. This study was rated B. No significant effect was found with combined vitamin D and calcium supplementation on any cardiovascular outcome. However, borderline nonsignificant associations were found for three outcomes, suggesting increased risk

with supplementation for a composite cardiac outcome, invasive cardiac interventions, and transient ischemic attacks. No significant associations were found for a composite cardiac outcome, coronary heart disease death, myocardial infarction, hospitalization for heart failure, angina, stroke or transient ischemic attack, and stroke alone.

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

Combined Vitamin D and Calcium and Body Weight

This outcome was not investigated for the current report.

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

Combined Vitamin D and Calcium and Cancer

Total Cancer

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

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

Colorectal Cancer

Only the B-rated WHI trial **identified for the original report** evaluated colorectal cancer. It reported no significant reduction in colorectal cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1,000 mg/d) compared with placebo. **A post hoc analysis of the WHI CaD trial identified for the current report that stratified participants by baseline use of personal vitamin D and calcium supplements found no difference in risk for colorectal cancer by previous or additional supplement use.**

Colorectal Polyps

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

Breast Cancer

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

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

Preeclampsia

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

Other Outcomes

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

Combined Vitamin D and Calcium and Bone Health

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

Rickets, Fractures, Falls, or Performance Measures

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

The current report identified one new RCT and one reanalysis of the WHI CaD trial that examined the effect of an intervention with vitamin D and calcium on osteoporotic fracture risk among postmenopausal women. The reanalysis of data from the WHI CaD trial compared the effects of the intervention between women who had been using personal vitamin D and/or calcium supplements at baseline. The primary outcome was risk for hip fracture at 5 or more years and secondary outcomes included other fractures. The reanalysis found that among women who were not taking calcium or vitamin D

supplements at baseline, the risk for hip fracture was significantly decreased (no effect was seen among women who had been taking supplements); it found no effect of the intervention on overall fracture risk in women who had been taking supplements or in those who had not (rated A).² The second RCT, the OSTPRE study, found no effect of 3 years' supplementation with calcium and vitamin D on risk for total, nonvertebral, distal forearm, upper extremity, or lower extremity fragility fractures among 3,195 postmenopausal women age 65 to 71 years (rated A).

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

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

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

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

Bone Mineral Density or Bone Mineral Content

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

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

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

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

Combined Vitamin D and Calcium and All-Cause Mortality

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

Combined Vitamin D and Calcium and Hypertension and Blood Pressure

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

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

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

The current report identified 1 new existing systematic review published since the original report that addressed the question as well as 18 new RCTs that met the inclusion criteria (2 that used fortified foods and the remainder that used supplements). The systematic review, based on 76 RCTs, reported widely varying increases in serum concentrations of 25(OH) for similar doses of vitamin D, with a general increase in serum concentration with supplement administration. Of the RCTs identified for the current report that met the criteria for inclusion in an assessment of dose response, all reported increases in serum 25(OH)D with supplementation; however, the findings varied by age group and health status of participants, baseline serum 25(OH)D concentration, dose, duration, and assay used to assess serum 25(OH)D. Only one study used the National Institute of Standards and Technology vitamin D as a reference standard, and six reported

participating in the Vitamin D External Quality Assessment Scheme. Of 54 RCTs included in the original and the current report, only 4 reported the year the assays were conducted.

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

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

Stratification of Key Outcomes by Vitamin D Assay Method

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

Outcomes for Tolerable Upper Intake Levels

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

Renal Outcomes

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

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

^a HPLC is high pressure liquid chromatography.

Adverse Events Reported in RCTs

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

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

Five new studies reported on gastrointestinal symptoms, of which only one included supplemental calcium. Two new studies reported on serious adverse events, including one death, cancer diagnoses, and acute surgeries, which were more prevalent in the placebo group and thus could not have been related to the use of vitamin D.

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

Summation

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

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

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

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

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

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

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

For prostate cancer, three of four cohort studies **identified for the original report** found significant associations between higher calcium intake (>1,500 or >2,000 mg/day) and increased risk of prostate cancer, compared with men consuming lower amount of calcium (500–1,000 mg/day). **Studies of calcium alone were not included in the updated report.**

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

Taken together, six cohort studies of calcium intake suggest that in populations at relatively increased risk of stroke and with relatively low dietary calcium intake (i.e., in East Asia), lower levels of calcium intake under about 700 mg per day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the United States, and one Finnish

study found a possible association of increased risk of stroke in men with calcium intakes above 1,000 mg. **Again, studies of calcium alone were not included in the current report.**

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

For the current report, we abstracted the methods used to assay serum 25(OH)D for all RCTs included in the assessment of dose-response, as well as the RCTs included in the original report and plotted dose response according to assay method. Although most studies employed radioimmunoassays, some relied on other immunoassay methods, receptor binding assays, and HPLC/tandem mass spectrometry. To characterize the assay methods more completely, we also noted the country and year in which the assay was performed, when reported, and any information provided on standardization; however, very few studies reported the year assays were conducted or how assays were standardized. Combined with the evidence regarding the significant effect of season of blood draw on serum 25(OH)D concentrations, this lack of information on year of assay renders comparing or combining outcomes challenging, even when the same type of assay was used.

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

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

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

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

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Muscle strength/falls	None included	None included	Conclusions based on 2006 Ottawa EPC report were mixed	(2 RCTs on fall risk in elderly) 1 reported no effect; 1 reported effects only in subgroups) (2 RCTs on muscle strength) both showed positive effects but one showed effects only in those with lower serum 25(OH)D	(1 prospective cohort on falls) inverse association of 25(OH)D and falls risk (4 prospective cohort studies on muscle strength) ¾ showed inverse association of 25(OH)D with muscle strength	Both original and newer studies had mixed results
Bone Health Vitamin D+Ca						
Rickets	None identified	None identified		None identified	None identified	
BMD/BMC	(3 RCTs) 1 RCT in healthy girls showed no effects on BMC; 2 RCTs in postmenopausal women showed positive effects on BMD	None included	Ottawa EPC report concluded that overall, there is good evidence that vitamin D+Ca resulted in small increases in BMD of the spine, total body, femoral neck, and total hip	(7 RCTs) 2 RCTs in girls and young women showed positive effects; 4 RCTs in post- menopausal women had mixed effects; 1 RCT in men showed no effects	None included	Both original and newer studies had mixed results

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Fracture	(1 RCT) Vitamin D+Ca reduced risk of stress fracture among premenopausal women	None identified	Ottawa EPC report concluded that supplementation with vitamin D +calcium is effective in reducing fractures in institutionalized populations	(1 RCT and 1 post-hoc analysis, both rated A) Post-hoc analysis of year-7 WHI data showed significantly decreased risk for hip fracture (but not overall fracture) among women who did not use personal supplements at baseline; 3-year study of postmenopausal women found no effect on fracture at any site	None identified	General agreement among original Ottawa EPC report, 2009 report, and current report that vitamin D+Ca reduces risk for some fractures but not consistent across fracture types or populations. Post-hoc analysis of WHI data demonstrates need to consider baseline supplement use.
Muscle strength/ falls	(1 RCT) 5-year analysis of WHI subsample found no effect on performance	None included	Ottawa EPC report found evidence that supplemental vitamin D reduces falls in postmenopausal women and effect for older men is inconsistent	(1 RCT on muscle strength/1 RCT on falls) no effects of vitamin D+Ca on muscle strength or fall risk	None identified	2009 report consistent with current report that vitamin D+Ca supplementation does not affect risk for falls or muscle strength but too few studies to draw firm conclusions

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Pregnancy- Related Outcomes Vitamin D						
Birth weight/ length (infancy)	(7 RCTs) 2 out of 7 studies (from same center) reported significant effect of supplement on birth weight; 5 reported no effects	(2 prospective cohorts) no effects	Diverse populations and methodological approaches precluded conclusions	(5 RCTs) 1 out of 5 reported significant effect of supplement intake on birth weight and length; remaining 4: no effect	(2 prospective cohorts) half observed association of 2nd trimester maternal serum 25(OH)D with birth weight	Only 1 C-rated RCT observed an effect of vitamin D; compliance was a challenge in several RCTs
Small-for gestational age (SGA)	No studies identified	No studies identified	NA	No studies identified	(2 prospective cohort studies) 1 found an inverse association of serum 25(OH)D with risk for SGA; the other found a U-shaped association	Differences in observations between studies
Preterm birth	No studies identified	No studies identified	NA	No studies identified	(1 prospective cohort study and 1 nested case-control) the prospective cohort observed an inverse association with risk, the nested case-control observed no association	Differences in observations among studies

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Preeclampsia	No RCTs identified	(1 nested case-control) study observed an association between serum 25(OH)D <37.5 nmol/L and increased risk for preeclampsia	Studies too small in number to reach conclusions	(2 RCTs (pooled in one article)) vitamin D supplementation (4000IU/d but not 2000IU) reduced the risk for preeclampsia	(7 observational studies (5 nested case-control and 2 prospective cohort)); 5 of 7 studies observed an association between serum 25(OH)D<50nmol/L and increased risk for preeclampsia	Newer studies suggest possible effect of serum 25(OH)D concentration or vitamin D supplementation on reducing risk for preeclampsia
Pregnancy-Related Outcomes Vitamin D + Ca						
Birth weight/length (infancy)	(1 C-rated nonrandomized trial) study found significant effect of vitamin D+Ca supplementation on birth weight	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings
SGA	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preterm birth	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preeclampsia	(1 C-rated RCT) Study found no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) on prevention of preeclampsia	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
All-Cause Mortality						
All-cause mortality Vitamin D	(1 RCT and reanalysis of existing SR) vitamin D supplementation had no significant effect	(4 cohort studies): 3 reported no association; 1 reported a trend toward an inverse association	No relationship of vitamin D with all-cause mortality	None identified	(25 observational studies) 7 reported no association; 16 reported an inverse association; 2 reported a U- shaped association	Both the 2009 and the current report suggest no relationship of vitamin D with all-cause mortality
All-cause mortality Vitamin D+Ca	(reanalysis of existing SR) vitamin D+Ca supplementation had no significant effect	None identified	No relationship of vitamin D+Ca and all-cause mortality	None identified	None identified	No literature on vitamin D+Ca and all-cause mortality
CVD Vitamin D						
Hypertension	None identified	(2 observational studies) 2 large prospective cohort studies observed a significant inverse association of serum 25(OH)D with risk for hypertension	Too few studies to draw conclusions	None identified	(2 observational studies) 1 C-rated prospective cohort study observed an inverse association between serum 25(OH)D and risk for hypertension; 1 A-rated cohort study observed a j-shaped association with risk for hypertension	Relative agreement between 2009 report findings and current report except for observed j- shaped association between serum 25(OH)D and hypertension risk

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Blood pressure	(3 RCTs) 3 trials reported no effect of vitamin D on diastolic blood pressure, but diastolic pressure was decreased in 1 study, unchanged in 1, and increased in 1			(10 RCTs) 7 reported no effect, vitamin D decreased blood pressure in 2 studies, and vitamin D increased systolic blood pressure in 1	None included	2009 report and current report agree that effects of vitamin D supplementation on blood pressure are inconsistent, based on small numbers of studies
CVD events	(1 RCT) No effect of vitamin D supplementation on risk for CV events in elderly	(4 cohort studies) 2 studies reported a significant inverse association between serum 25(OH)D and total CV events; 2 studies reported no associations	Mixed effects reported	None identified	(1 SR of prospective studies; 7 new studies) SR found significant inverse association of serum 25(OH)D and CV events; new cohort studies found mixed effects	Associations of serum 25(OH)D with CVD events observed in some cohort studies but not all and not supported by RCTs
CVD mortality	(1 RCT) No effect of vitamin D supplementation on risk for CV death in elderly	None included	Too few studies to draw conclusions	None identified	(7 cohort studies, 1 nested case-control) Increased risk for cardiovascular death for those with the lowest serum 25(OH)D concentrations compared with the highest	Mixed findings between 1 RCT in 2009 report and 8 observational studies identified for current report

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
CVD Vitamin D+Ca						
Hypertension	(1 RCT) The WHI reported no effect of vitamin D+Ca supplementation on hypertension risk	None identified	No effects reported; small number of trials	None identified	None identified	2009 report and current report identified no effects
Blood pressure	(2 RCTs) No effect of supplementation seen on blood pressure at short or long followup times	None included	No effects reported; small number of trials	None identified	None included	2009 report and current report identified no effects
CVD events	(1 RCT) WHI CaD Trial 7-year followup found no effect on any CV outcome, but a trend toward increased risk for a composite cardiovascular outcome with supplementation	None included	No significant effects of Vitamin D+Ca but trend toward increasing risk of CV events with supplementation	(1 post-hoc analysis of the WHI trial) no effect of study supplements (400IU vitamin D ₃ and 1000mg Ca) alone on risk for CV events at >5 years followup	None identified	Post-hoc reanalysis of WHI CaD outcomes by use of personal supplements at baseline finds no effect of study intervention on risk for CVD

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Cancer Vitamin D						
Total cancer/ cancer mortality	(2 RCTs) no effect of vitamin D supplementation on risk for cancer mortality	(1 cohort study) analysis of NHANES III found no association between 25(OH)D status and risk for cancer mortality		No new RCTs identified	(2 cohort studies assessed association with cancer incidence) no association of 25(OH)D and total cancer incidence (10 cohort studies and 1 nested case- control assessed association with total cancer mortality) 5 cohort studies saw no association; 3 cohorts and the nested case-control observed a trend toward an inverse association; 1 observed a trend toward a positive association; 1 observed a U- shaped association	Totality of studies suggest no or complicated association of 25(OH)D status with cancer mortality

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Prostate cancer	No studies identified	(12 nested case-control studies) 8 studies found no association between serum 25(OH)D concentrations and prostate cancer risk; 1 study found a significant inverse association between lower baseline serum 25(OH)D concentrations (<30 compared with >55 nmol/L) and higher risk (rated C); another C-rated study observed a U-shaped association (C-rated)	Observational studies only; mixed findings on associations	No studies identified	(7 observational studies) 4 nested case-control studies and 1 cohort found no association of serum 25(OH)D with risk for prostate cancer; 2 nested case-controls observed a trend toward increasing risk with higher serum 25(OH)D concentrations	2009 and current report find observational studies only, with mixed findings on associations

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

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

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Cancer Vitamin D+Ca						
Total cancer mortality	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions
Prostate cancer	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions
Breast cancer	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for breast cancer	No studies identified		(WHI CaD post-hoc analysis) assessment of breast cancer risk among trial participants stratified by use of personal supplements at baseline reported a trend toward decreasing risk among women who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Colorectal cancer (CRC)	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for CRC	No studies identified	Too few studies to draw conclusions about supplementation	(WHI CaD post-hoc analysis) assessment of CRC risk among trial participants stratified by use of personal supplements at baseline reported no difference in risk between personal supplement users and those who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Pancreatic cancer	No studies identified	No studies identified		No studies identified	No studies identified	

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

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Immune Function Vitamin D						
Infectious illnesses	No studies identified	(2 observational studies) NHANES III found no significant association between serum 25(OH)D concentrations and infectious disease mortality		(4 RCTs) 4 RCTs of infants and adults reported no effects	(9 observational studies) 3 cohort studies observed an inverse association of cord blood 25(OH)D and risk for infections at 3–6 months; two cohort studies observed inverse associations among school-age children; 3 cohort studies of adults observed similar associations with various infectious illnesses	Number of studies in 2009 report too small to assess association of serum 25(OH)D with risk for infection; current report identified RCTs and observational studies, but no consistent effects or associations emerged
Autoimmune disorders	No studies identified	No studies identified	No studies on which to base conclusions	(1 RCT) a subgroup analysis of WHI CaD participants found no effect of supplementation on risk for rheumatoid arthritis	(4 observational studies) 3 nested case-control studies and 1 cohort study reported mixed associations of serum 25(OH)D concentrations with risk for type 1 diabetes; 1 study reported mixed associations of serum 25(OH)D with risk for multiple sclerosis	No studies in 2009 report on association of serum 25(OH)D with risk for autoimmune diseases; current report identified 1 RCT and observational studies, but no consistent effects or associations emerged

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

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

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

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

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

Introduction

Background

This systematic review of the literature constitutes an update of a systematic review that was conducted in 2009. This section describes the background of the original review and this update.

The Food and Nutrition Board of the Institute of Medicine (IOM), with funding from agencies and departments of the United States and Canadian Governments, recently completed their 10-year development of nutrient reference values entitled Dietary Reference Intakes (DRI).³ 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.⁴ 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 conducting 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.⁵ 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 of systematic reviews as a routine part of the DRI process.

Following these activities, a working group of United States 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.⁶ As a result of these conferences in March of 2008, the IOM convened a working group of United States 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.⁷ 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).⁸ They concluded that there was sufficient new data on bone health for several of the life stage 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.⁷ 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. **The result was the original report on which this current update report is based.**⁹

That original report formed a central portion of the evidence base the IOM committee to Review Dietary Reference Intakes for Vitamin D and Calcium of the Food and Nutrition considered in reviewing the 1997 DRI values for their 2011 update.

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decision-making for vitamin D in primary care, based on the updated DRI report, the ODS and AHRQ requested an update to the 2009 systematic review that will incorporate the findings of studies on vitamin D and vitamin D administered in conjunction with calcium that have been conducted since the release of the 2009 review. The aim of this update report was to assess many of the outcomes assessed in the original 2009 report, with the exception of outcomes pertaining to body weight and composition and postnatal growth. In addition, the current report did not update the findings on calcium supplementation and status alone, but limited itself to trials of supplementation with vitamin D with or without calcium and to observational studies on serum 25(OH)D concentrations.

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

Since the analysis for the original report was conducted, evidence has been growing regarding the lack of comparability of results among the various methods for assaying serum 25(OH). Assessing the body of evidence on the outcomes of vitamin D interventions and exposures requires an understanding of how the assay methods compare and the limitations inherent in cross-comparisons. Therefore, for any newly included studies on the effect of vitamin D supplementation on serum 25(OH)D concentrations as well as the studies included in the original report, this update report also provides the details of the vitamin D serum assay methodology, to permit a comparison by assay method.

The text of the original 2009 report has been preserved in its entirety; however, text and tables that report outcomes of calcium supplementation only have been omitted. Here and in the remainder of the report, updated findings are presented in boldface type. The protocol for the update report was posted on the AHRQ website for public comment which can be found at <http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529>.

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).^{10,11} There are two forms of vitamin D: vitamin D₃ (cholecalciferol), which is produced from the conversion of 7-dehydrocholesterol in the epidermis and dermis in humans, and vitamin D₂ (ergocalciferol) which is produced in mushrooms and yeast. The chemical difference between vitamin D₂ and D₃ is in the side chain; in contrast to vitamin D₃, vitamin D₂ 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 D₃ 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 hydroxylations 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 (PTH), together with serum calcium and phosphorus concentrations. Additional tissues that express the enzyme that catalyzes 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.¹²

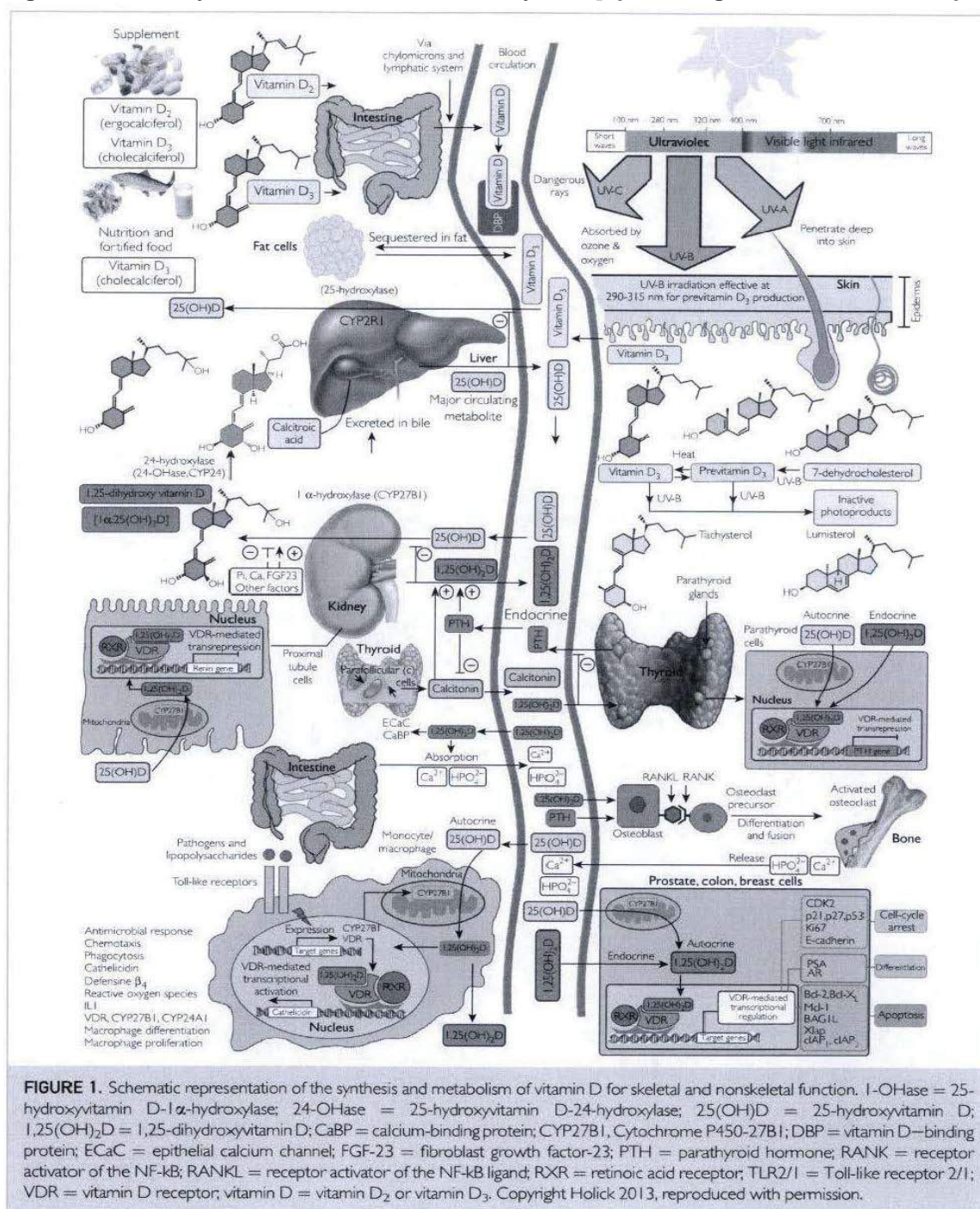
Vitamin D has both genomic and nongenomic functions. For the genomic functions, 1,25(OH)₂D interacts with nuclear vitamin D receptors to influence gene transcription. Nuclear receptors for 1,25(OH)₂D have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle, and skin. 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 PTH, 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 are influenced by vitamin D. Five biological systems have vitamin D receptors and are responsive to 1,25(OH)₂D, as summarized in Figure 1.¹³ 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, 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.¹⁴ A number of recent reviews have appeared on these topics.¹³⁻²¹

Figure 1. Summary of the vitamin D endocrine system [updated figure for the current report]



Reprinted from Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clinic Proceedings. 2013 Jul;88(7):720-55. PMID: 23790560 with permission from Elsevier.²¹

Sources, Metabolism, and Functions of Calcium

The major source of dietary calcium in the North American diet, but not necessarily other countries, is dairy products (about 70%). 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 $1,25(\text{OH})_2\text{D}$. This process occurs primarily in the duodenum and proximal jejunum, is saturable, is energy dependent and involves a calcium binding protein. The $1,25(\text{OH})_2\text{D}$ -dependent absorption of calcium is stimulated by low dietary calcium intakes. The other route of intestinal calcium absorption is independent of $1,25(\text{OH})_2\text{D}$ 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%), primarily albumin and prealbumin; complexed with sulfate, phosphate, or citrate (~10%); and in the ionized form (~50%). Blood calcium concentrations are controlled extracellularly by PTH, 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 balance 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]). $1,25(\text{OH})_2\text{D}$ plays a critical role in regulating plasma calcium concentrations through its role in intestinal calcium absorption, bone resorption, and renal calcium resorption. The 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.⁵ 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).²² 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 reviews 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.

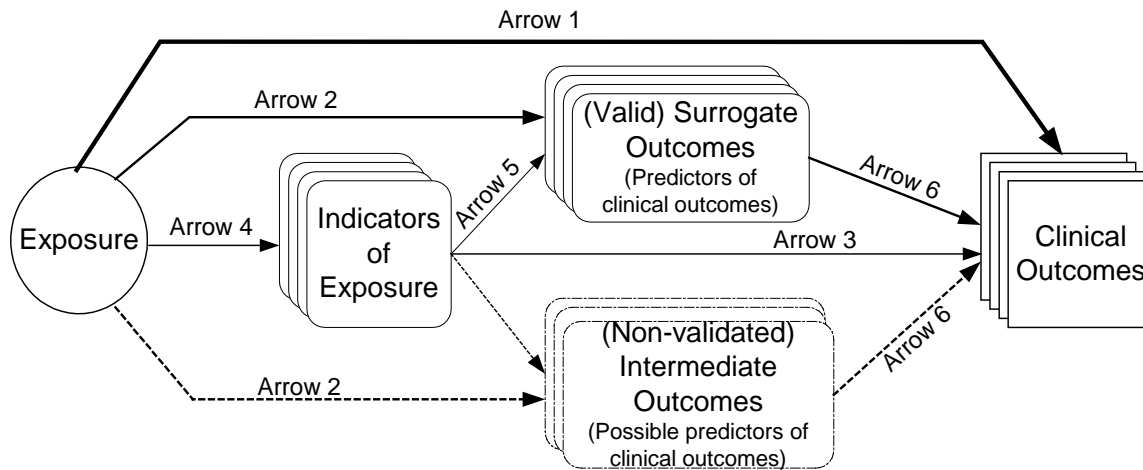
Key Questions Addressed in This Report

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 on 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 the Methods chapter. The intent of this report is not to make recommendations on specific outcomes nor specific values for DRIs 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 U.S. 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).⁵ The Key Questions are:

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

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 (**not included in the update**), 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, as discussed in the Methods chapter.

Methods

Overview

This report is based on **two** systematic reviews 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 Guide for Effectiveness and Comparative Effectiveness Reviews” (http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf). The initial questions identified by the federal sponsors of **the 2009** report were refined with input from a Technical Expert Panel (TEP). **The questions were modified slightly by the federal sponsor for the current report.** This report does not make clinical or policy recommendations. The original report was provided to an IOM committee charged with updating vitamin D and calcium DRIs.

A description of roles and responsibilities of **the original and current** sponsoring federal agencies, AHRQ, the TEP, and the EPCs 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 that are used, their explanations have been repeated whenever deemed necessary. A table of **Abbreviations** can be found after the references. We also provide a table with the latitudes of several major cities in Central and North America, right after the **Abbreviations** table.

Sponsoring Federal Agencies

The sponsoring agencies (**a single agency for the current report**) were responsible for specifying the topic-specific task order requirements. They participated in a kickoff 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 the Federal sponsor was limited to comments on factual errors, requests for clarification, and monitoring for 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

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 allow the EPC to focus on the scientific issues and activities.

Technical Expert Panel

The Technical Expert Panel (TEP) comprises qualified experts including, but not limited to, individuals with knowledge of DRI decisionmaking 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 DRIs. They did not have any decisionmaking role and did not participate in writing any part of the evidence report.

EPC Methodologists

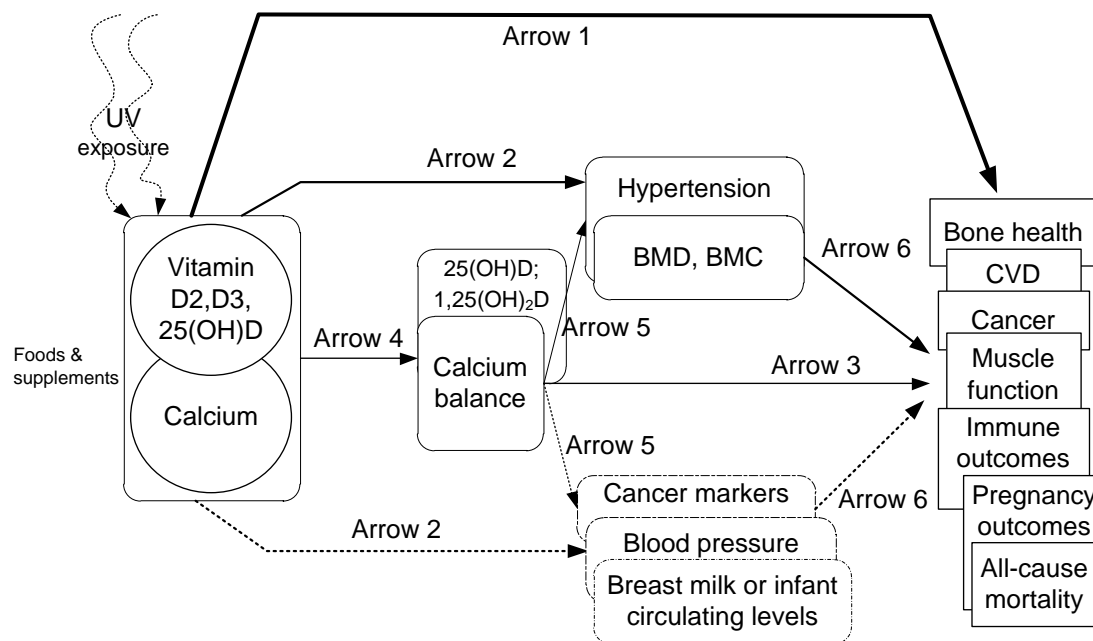
This evidence report was carried out under the AHRQ EPC program, which has a 16-year history of producing hundreds of evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continually refine approaches to conducting evidence reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. The Tufts EPC and RAND EPC have produced many evidence reports on nutrition topics.²³⁻³² (www.ahrq.gov/research/findings/evidence-based-reports/index.html). 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 DRIs, using vitamin A as an example.⁵

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 (**excluded in the update report**), 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 the Introduction 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, Interventions (or Exposure in the case of observational studies), Comparators, and Outcomes of interest. Details are described in the sections that follow.

Figure 3. Analytic framework for vitamin D with or without calcium: EARs [revised for the current report]



EARs

Arrow 1: Association of exposure with clinical outcomes of interest.

Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have, respectively, good or possible evidence for linkage with clinical outcomes). (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.

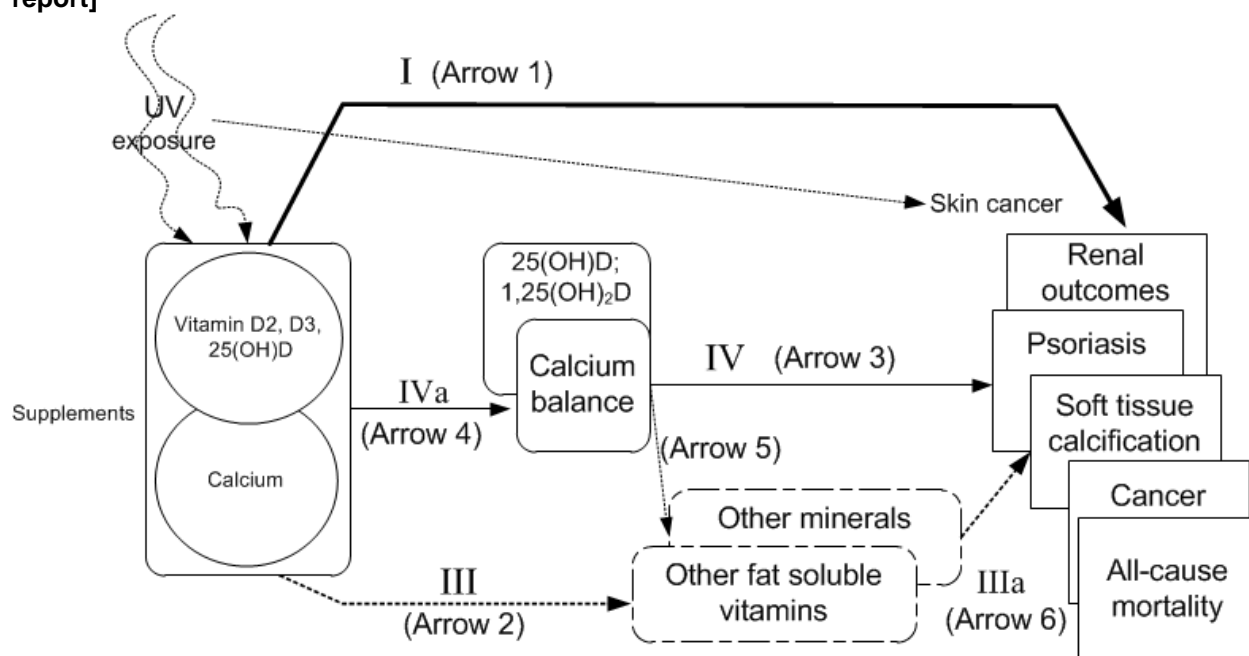
Arrow 4: Association between exposure and indicators of exposure.

Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes.

Arrow 6: Association between surrogate or intermediate outcomes and clinical outcomes.

Abbreviations: 1,25(OH)₂D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; BMC = bone mineral content; BMD = bone mineral density; CVD = cardiovascular disease; UV = ultraviolet light

Figure 4. Analytic framework for vitamin D with or without calcium ULs [revised for the current report]



Arrow 1: Association of exposure with clinical outcomes of interest.

Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have, respectively, good or possible evidence for linkage with clinical outcomes). (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.

Abbreviations: 1,25(OH)₂D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; UV = ultraviolet light

Definitions

Vitamin D and Calcium Exposures

Vitamin D exposure included intake of vitamin D₂ or vitamin D₃ from foods and supplements, including human milk and commercial infant formulas. Because the primary source of vitamin D in the human body is from 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.²² 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 as fulfilling 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 the “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 DRIs 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 the 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 the “Eligibility Criteria” section. **The questions shown reflect the revisions for the update report.**

Key Question 1. What is the effect of vitamin D, calcium **(excluded from update report)**, 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 **(the update report excludes the outcomes of postnatal growth and weight outcomes)**? (Arrow 1 in Figure 2)

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

Key Question 3. What is the association between serum 25(OH)D concentrations or calcium balance **(excluded from update report)** and clinical outcomes? (Arrow 3 in Figure 2)

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 in Figure 2)

Key Question 5. What is the association between serum 25(OH)D concentrations and surrogate or intermediate outcomes? (Arrow 5 in Figure 2)

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.⁸ 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).

The search strategy of peer-reviewed literature for the update report duplicated that used in the original 2009 report to the extent possible, excluding the searches specific to calcium only and those for the outcomes of growth and weight. The librarian at the RAND Southern California Evidence-based Practice Center reviewed and modified the search strategies as needed and ran the searches in Medline® and the Cochrane Central Database from January 2008 to December 30, 2013 (see Appendix A).

In addition, at the request of AHRQ, in lieu of contacting each U.S. manufacturer of vitamin D supplements for product information and results of any unpublished studies, a notice was placed in the *Federal Register* on Thursday, July 18, 2013, requesting scientific information submissions (<https://www.federalregister.gov/articles/2013/07/18/2013->

17177/scientific-information-request-on-vitamin-d-and-calcium). **One draft journal article submission was received.**

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 **[for the update, we sought only studies of vitamin D or vitamin D and 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% 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% with 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)₂D concentration
- Dietary intake level of vitamin D were not included due to inadequacy of nutrient composition tables for vitamin D.³³
- Dietary intake level of calcium from food and/or supplements **[excluded for update]**
- Calcium balance (i.e., calcium accretion, retention, and loss) **[excluded for update]**
- For interventional studies:
 - Vitamin D supplements (but not analogues) with known doses
 - Calcium supplements with known doses **[for update, only if accompanied by vitamin D or administered as part of placebo]**
 - 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 could 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 **[excluded from update]**
 - 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 **[excluded from update]**
 - 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
 - Falls 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 in 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 and 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. Where there were several systematic reviews, each of which included only a sample of the total literature included by the several systematic reviews, all systematic reviews were included.

Other Specific Eligibility Criteria

- Growth outcomes (weight and height gain) **[excluded from update]**
 - 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 [**only vitamin D or vitamin D and calcium for update**] 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 report⁸ 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 report⁸ 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 did 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. **For the update, we extracted data from all original studies that satisfied the**

inclusions/exclusion criteria and were published since the original 2009 report. For a small number of outcomes, we identified and report the conclusions of systematic reviews that we determined to be of high quality.

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 (**including location and date of assay performance; manufacturer of kit, if used; coefficients of variation; and reference standard, if described [the reference standard refers to a sample whose concentration of 25(OH)D has been ascertained by a recognized entity, such as the United States National Institute of Standards and Technology (NIST), that is used to establish the reliability of an assay]**), 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 (D₂ or D₃) was clearly reported, we extracted and reported this information. Otherwise, we used the general term “vitamin D”. **For the update, DistillerSR™ was used for data extraction.** 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 AMSTAR³⁴ 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.

All data abstracted for the report will reside on the Systematic Review Data Repository; data for the 2009 report currently reside at this site.

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. **For the update, we reported the data for dose-response outcomes by assay method, to the extent the assay method could be identified from the study report. A table of assay methods, locations, dates, precision, and standards for each controlled trial included in the original and update reports appears in Appendix G. Key outcomes stratified by assay method are shown in Appendix H.**

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 SE₁, SE₂, and SE₁₂ are the SEs for baseline, final and change, respectively, and ρ is the correlation between the baseline and final measurements.³⁵ 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 the large degree of clinical and methodological heterogeneity across studies. However, **the original report** reanalyzed an existing meta-analysis using available data in the all-cause mortality section. **That report** performed random effects model meta-analyses of risk ratios using the DerSimonian and Laird model.³⁶ 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. Heterogeneity was tested using Cochran's Q (considered significant for $P < 0.10$) and quantified its extent with I^2 .^{37,38} 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 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. Although the quality of evidence is multidimensional and a single metric cannot adequately capture information needed to interpret a study, it is desirable to have a simple evidence grading system using a single quantity. The grading system employed for AHRQ EPC reports was adapted as described below.

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 CONSORT³⁹ 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 follow up between the compared groups or overall high loss to follow up. 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 studies based on some of the reporting items for cohort study in STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist⁴⁰ and the nutrition-specific items in our previous publication.⁴¹ 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:

Grade 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.

Grade 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.

Grade 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 Decisionmaking

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 DRIs, 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 verified the diagnoses independently (e.g., by medical records or pathological reports). An observational study of cancer outcomes could not receive grade A if the cancer diagnoses were not verified independently. We also examined if the study adequately controlled for other risk factors for the specific cancer. We used the suggested risk factors by American Cancer Society (www.cancer.org). An observational study of cancer outcomes could not 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,³⁴ 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 for 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 lifestyles) were controlled for, we marked "X" in that category. Otherwise, the category was left blank. **The full list of potential confounders for which new studies for this update controlled are listed with those studies in the evidence tables in Appendix C.**

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 a 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) **both in the original 2009 report and in the current report** 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; **Figure 15 shows the data for the effects of vitamin D administration on serum 25(OH)D concentration as a series of bubble plots for each assay method, and Table 67 shows the assay method for the studies included in the dose response figures. In Appendix G of this update report, we provide a table of the assay methods; detailed information on the kits used, if noted; reference citations for assay methods; locations and dates of assay; precision; and reference standards, if reported, for randomized controlled trials included in both the original report and the update. In particular, we note whether studies employed reference standards such as the NIST standard or reported participating in the Vitamin D External Quality Assessment Scheme (DEQAS). Finally, in Appendix H, we stratify by assay method all summary and outcomes tables for key outcomes (defined for this report as any outcomes reported in three or more RCTs or eight or more observational studies).**

Sunlight Exposure

The original report included 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 (located after the **Abbreviations** table).

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 in the summary tables. More details on the reporting characteristics of individual studies and systematic reviews are found in the evidence tables (Appendix C).

Peer Review and Public Commentary

Experts were invited to provide external peer review of the update report. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We received comments back from six reviewers and one public commenter. We have addressed all peer and public comments, revising the text as appropriate, and have documented all responses in a “disposition of comments report” that will be made available 3 months after the Agency posts the final report on the AHRQ website.

Results

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

The findings of the studies identified for this update report are in boldface type in the text and summary tables.

Literature Search Results

For the 2009 report, 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 F); thus, a total of 165 primary study articles met the inclusion criteria and were included in this report (Figure 5a). 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 1,746 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 5a).

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.

For this update, the original MEDLINE® and Cochrane Database searches yielded 6,154 titles for EAR and UL outcomes, combined. An additional 11 titles were identified from reference mining and hand searching, for a total of 6,165 titles and abstracts that underwent dual review. Of this 6,165, 5,058 abstracts were rejected and 1,107 went on for full text review. Of that 1,107, 10 were identified as background, 772 failed to meet inclusion criteria and were rejected, and 154 articles with 156 studies went on for detailed abstraction and are included in this report (Figure 5b). In addition, 171 systematic reviewers were looked at of which 2 were included in the update report

Figure 5a. Literature flow for the original report

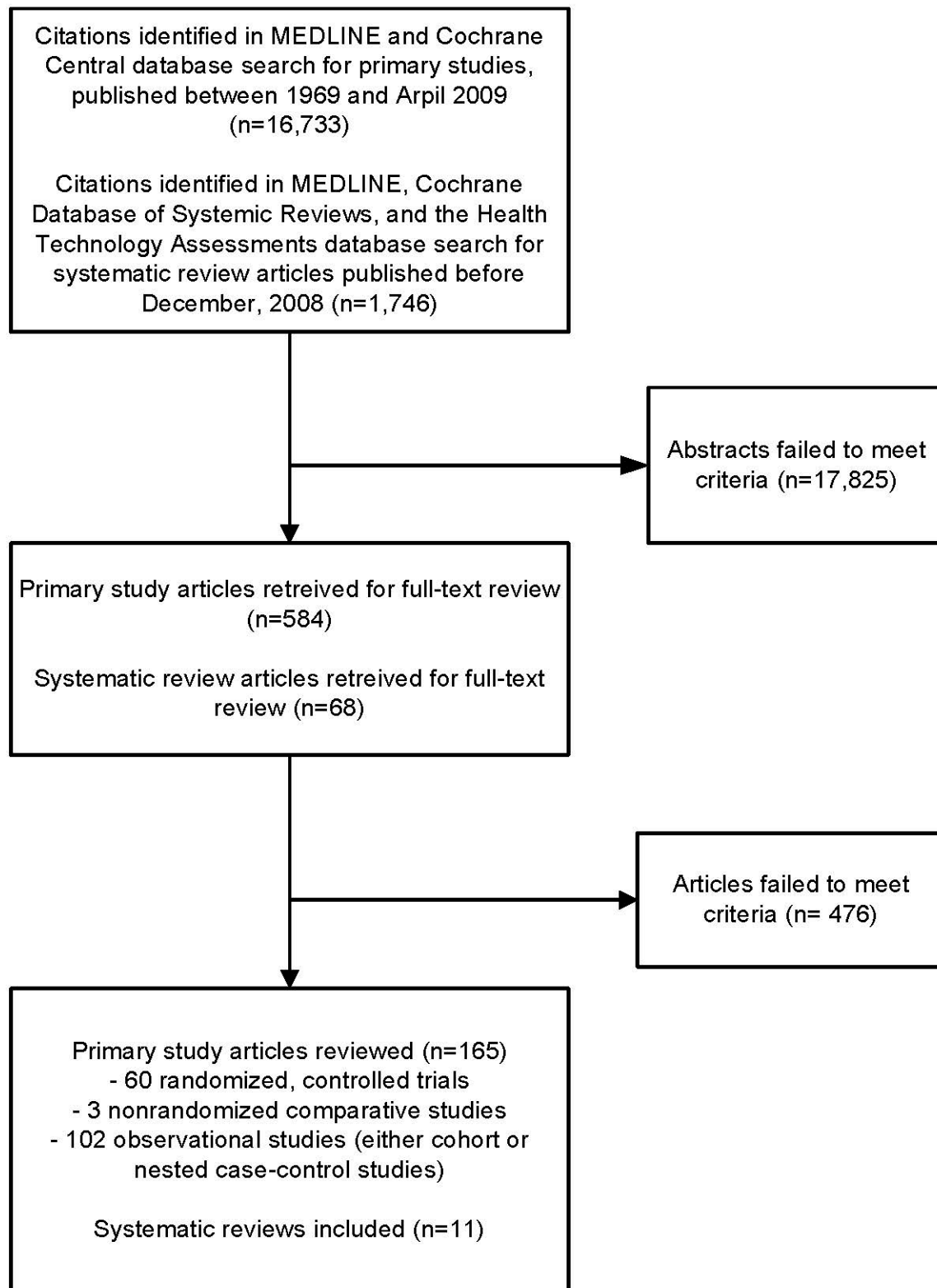


Figure 5b. Literature flow for the current report

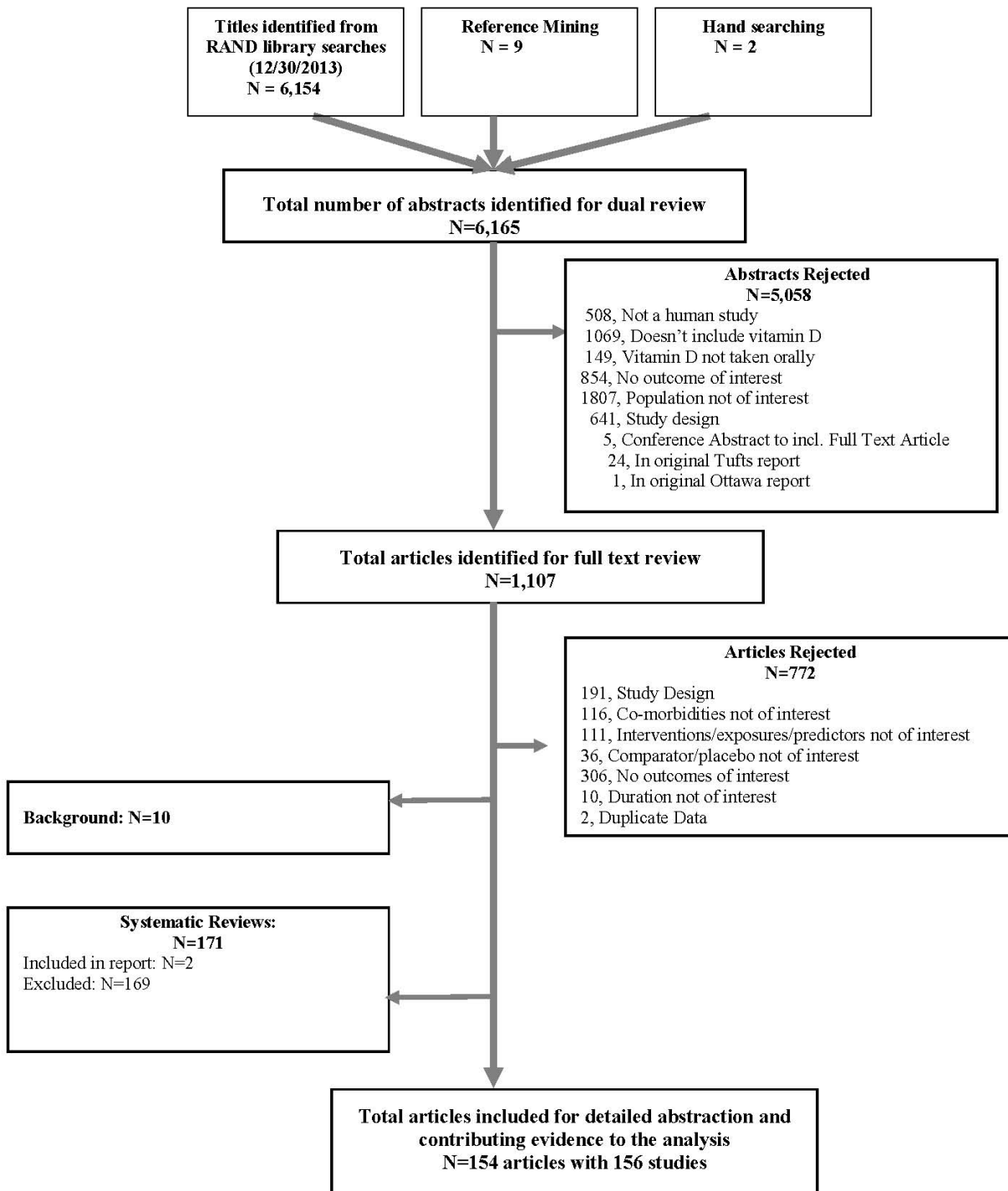


Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages [updated for the current report]

	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										5				1		
7 mo–2 y	1										4 ^B						
3–8 y											7						
9–18 y	3			1							8			2	5		
19–50 y		19	1	9	6	3		8		1	9		10	3	6	3	8
51–70 y		31	2	14	17	11	1	11		4	7		31	13	5	3	5
≥71 y		20		10	5	5		4		1	3		26	17	1	2	5
Pregnant & lactating women	16										6	9					
Postmenopause		4	1	2		1		1	2		2 ^B		2	3	3	1	4
Total unique studies per outcome	18	36	3	16	19	14	1	12	2	4	27	9	34	22	12	4^C	13
[Total number of RCTs per outcome]	[10]	[1]	[3^A]	[2]	[0]	[1]	[0]	[0]	[1]	[0]	[7]	[1]	[8]	[9]	[12^A]	[0]	[13^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

Note: 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.

Abbreviations: CVD = cardiovascular disease; RCT = randomized controlled trial

^AOnly RCTs were eligible for this outcome.

^BRelationship between maternal 25(OH)D concentration and atopic eczema in infants.

^C1 study was a combined analysis of Nurses' Health Study and Health Professionals Followup Study.

Table 2. Number of primary studies on calcium intake and specific health outcomes that could be applicable to certain life stages [not updated in the current report]

	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																
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	14	1			[0]	[5^A]
Systematic reviews (unique studies) per outcome	1	0	3	0	0	1	1	0	0	0	0	1	0			0	6
	(17)		(41)			(2)	(2)					(12)					(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.

^AOnly RCTs were eligible for this outcome.

^BAssociation between total calcium intake in childhood and colorectal cancer after 65 years of followup.

^C1 study was a combined analysis of Nurses' Health Study and Health Professionals Followup Study.

^D6 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 [updated for the current report]

	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															3		
19–50 y			1											1	3		1
51–70 y		1	1	1		1	1	1		1			3	3	5	1	1
≥71 y			1	1		1		1		1			8	2	3		
Pregnant & lactating women	1											1					
Postmenopause		2	1	4		2	1	2		1			9	2	6	1	1
Total unique studies per outcome	1	2^B	2^B	4^B	0	2^B	2^B	2^B	0	1	0	1	12^{BC}	6^B	11	1^B	2^B
[Total number of RCTs per outcome]		[2]	[2^A]	[4]		[2]	[1]	[2]		[1]			[12]	[6]	[11^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.

^AOnly RCTs were eligible for this outcome.

^BIncluding the Women's Health Initiative (WHI) trial.

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

The original report reviewed primary studies that evaluated relationships between vitamin D and growth parameters in infants and children. That topic was not updated in the current

report; only the original findings are reported here for those outcomes. **The current report did review the evidence on the outcomes of birth weight and length.**

Synopsis

For the current report, we identified five RCTs (reported in four articles) and two observational studies that evaluated intake of or exposure to vitamin D, respectively, on birth weight and/or length. One of the five RCTs found a significant association of maternal vitamin D intake from supplements with birth weight and birth length; one of the four remaining studies was not powered to measure differences in birth weight or length; the remaining three observed no difference. Of the two observational cohort studies, one observed a significant association of second trimester maternal 25(OH)D concentrations and one found no association.

In the original report, 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)

In the current report, five RCTs (reported in four articles)^{1,42-44} reported on the effect of vitamin D supplementation during pregnancy on birth weight and/or length. Two cohort studies reported on the association between maternal serum 25(OH)D concentration and birth weight and/or length.^{45,46} The number of participants in the RCTs ranged from 140 to 504; the two cohort studies followed 1,113 and 2,146 mother-infant pairs. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400IU per day at 16 weeks gestation or earlier into three groups, who were given an addition 0, 1,600, or 3,600 IU vitamin D per day through the remainder of gestation; the study found no difference in birth weight among interventional arms (rated A).¹ The second study, a pseudo-RCT conducted in India, divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D, and the other received two doses of 3,000 micrograms vitamin D. A group of untreated women who were 24 week pregnant or more served as the controls. Both of the treated groups gave birth to infants who were significantly heavier than the usual care group ($p=0.003$) (rated C, largely attributable to incomplete reporting and the fact that the study was not a truly randomized study).⁴³ The third RCT, the AViDD study, conducted in Bangladesh randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes (rated A).⁴⁴ For the fourth and fifth studies, data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D₃ Supplementation studies, in which pregnant women were randomized to receive 0, 2000, or 4000 IU vitamin D per day in addition to their prenatal vitamins, were analyzed in combination: No differences were observed in birth weight among the groups (rated B).⁴²

In the original report, six RCTs⁴⁷⁻⁵³ and one nonrandomized comparative study⁵⁴ 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.^{55,56} 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 38° to 51°. 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. Follow up 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

For the current report, five RCTs (reported in four articles) were identified that administered supplemental vitamin D to pregnant women and assessed the effect on birth weight of the offspring. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400IU per day at 16 weeks gestation or earlier into three groups, who were given an addition 0, 1600, or 3600IU vitamin D per day through the remainder of gestation (assignment to the interventions was only partially random: Baseline serum 25(OH)D partly determined assignment); the study found no difference in birth weight among interventional arms.¹ A pseudo-RCT conducted in India divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D, and the other received two doses of 3,000 micrograms vitamin D. A group of untreated women who were 24 week pregnant or more served as the controls. Both of the treated groups gave birth to infants who were significantly heavier than the usual care group (p=0.003).⁴³ A third RCT, the AViDD study, conducted in Bangladesh randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes. Data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D₃ Supplementation studies, in which pregnant women were randomized to receive 0, 2000, or 4000 IU vitamin D per day in addition to their prenatal vitamins, were analyzed in combination: No differences were observed in birth weight among the intervention groups.⁴² Two cohort studies assessed the effects of maternal serum 25(OH)D concentrations on birth weight in the United States. One study of 1,113 mother-infant pairs assessed the association between second trimester 25(OH)D and birth weight and the effect of race. No association was seen between quartile of maternal 25(OH)D and birth weight; but the higher risk for low birth weight among black mothers was reduced significantly when adjusted for maternal 25(OH)D (study rated A). The other cohort study, of 2,146 mother-infant pairs found a significant association between low serum 25(OH) D concentrations and lower birth weight (study rated B).⁴⁶

In the original report, 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.^{47,51} There were twice as many low birth weight infants (<2500 g) in the control group compared to the supplemented group (21.7% vs. 11.9%); however, this difference

was not significant. A study from U.S. 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.⁵² 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.⁴⁹ 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 D₂ in 7th and 8th month) during the third trimester. The newborns' birth weight was significantly increased compared to those from 100 unsupplemented expectant mothers (difference 190 g).⁵⁰ 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.⁵⁴ 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.⁵³ 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.⁵⁶ 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.⁵⁵

9–18 Years

One RCT of vitamin D₃ (placebo, 200, or 2000 IU/d for 1 year) on girls in Lebanon aged 10–17 years found no significant difference at 1 year follow up in weight or height among the 34 girls who were premenarchal at time of enrollment.⁴⁸

Findings by Life Stage

- **0–6 mo**

For the current report, the results for birth weight and length are reported above.

In the original report, 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 affected 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 D₃ (placebo, 200, or 2000 IU/d for 1 year) on girls 10–17 years old found no significant difference at 1 year follow up 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: The results for the current study are reported above.**
For the original study, 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 affected 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 and growth outcomes: Characteristics of interventional studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Comparisons Vitamin D Data	Compliance	Comments
RCTs				
Maxwell 1981 ⁵¹ Brooke 1980 ⁴⁷ UK (51°N) [6793058] [6989438]	<ul style="list-style-type: none"> • Health status pregnancy • Mean age (range/SD), y nd • Male (%) 0 	25(OH)D at 28–32 wk: 20.1 nmol/L	Vit D 1000 IU/d 3 rd trimester only	nd First generation Asian immigrants only
Feliciano 1994 ⁴⁹ China (22°N to 47°N) [8078115]	<ul style="list-style-type: none"> • Health status healthy term • Mean age (range/SD), y newborn • Male (%) 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 ⁴⁸ Lebanon (33°N) [16278262]	<ul style="list-style-type: none"> • Health status healthy • Mean age (range/SD), y 13.2 (10–17) • Male (%) 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 ⁵² Charleston, US (32°N) [17661565]	<ul style="list-style-type: none"> • Health status Fully lactating; <1 mo postpartum • Mean age (range/SD), y 29 • Male (%) 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 ⁵⁰ India (28°N) [3243609]	<ul style="list-style-type: none"> • Health status no pregnancy-related complications • Mean age (range/SD), y 24 • Male (%) 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 7 th & 8 th mo) vs. no supplement	nd
Mallet 1986 ⁵³ France (48°N) [3755517]	<ul style="list-style-type: none"> • Health status pregnancy • Mean age (range/SD), y newborn • Male (%) 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 ⁵⁴ India (28°N) [7239350]	<ul style="list-style-type: none"> • Health status no pregnancy-related complications • Mean age (range/SD), y nd • Male (%) 0 	Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d	Vit D 1200 IU/d + Ca 375 mg/d (3 rd trimester) or Vit D 1.2 mil IU (total; 600,000 IU in 7 th & 8 th mo) or no supplement	nd

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
New Studies					
Hollis, 2011 ¹ Charleston, US	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), 0% y • Male (%) 	Healthy 27 (18–41/5.6) serum: delivered group- 59.5 23.8 nmol/L (6.0–172.5) exited group- 50.5 25.1 nmol/L (6.5–120.5) vit D intake: 400 IU group- 181.6 +/- 108.4 IU/d, 2000 IU group- 195.8 +/- 135.0, 4000 IU group- 204.2 +/- 148.2 calcium intake: 400 IU group-1063.6 +/- 539.6 mg/d, 2000 IU group- 993.9 +/- 514.0 mg/d, 4000 IU group- 1073.6 +/- 491.9 mg/d	Birth weight: Vit D 4000 IU vs. Vit D 2000 IU vs. Vit D 400 IU	69% (400-IU group), 68% (2000-IU group), and 69% (4000-IU group, p¼0.9)	Assignment to the interventions was only partially random: Baseline serum 25(OH)D also partly determined assignment
Kalra, 2012 ⁴³ India	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), 4.0 y • Male (%) 	nd 26.7 (SD 4.0) 0%	Table 2: Group 1 – 31.7 nmol/L (14.0–57.2) Group 2– 32.0 nmol/L (14.5–45.7)	Birth weight: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester) Length at Birth: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester)	nd

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Roth 2013 ⁴⁴ Bangladesh	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	Healthy 22.4 (SD 3.5) 0%	Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l	Birth weight: 35000 IU Vit D3 3rd trimester vs. Placebo Length at birth: 35000 IU Vit D3 3rd trimester vs. Placebo	99.2 ± 2.7%
NEW Cohort study					
Wagner 2013 ⁴² US	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	nd 27 (18–41) 0%	61.5 nmol/L	2000 IU vit D3 vs. 4000 IU vit D3 vs. control	NR

Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments		
				Nutrients	Demographics	Anthropometri c Measures	Medical	UV Exposure	Lifestyle			
Morley 2006 ⁵⁶ Australia (38°S) [16352684]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	singleton pregnancy; no disease 29 0	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA winter & summer	Length and weight in offspring stratified by mother's 25(OH)D	0	X	X	0	X	X	99% white; excluded dark skin or women with concealing clothing
Gale 2008 ⁵⁵ PAHSG UK (50°N) [17311057]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	singleton pregnancy <17 wk 26.3 0	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA nd	Length and weight in offspring stratified by mother's 25(OH)D	0	X	0	0	X	0	White only
New Studies												
Burris 2012 ⁴⁵ Massachusetts, US	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	nd 33 (SD 4.5) 0%			Weight in offspring stratified by mother's 25(OH)D	0	X	X	0	X	0	
Gernand, 2013 ⁴⁶ US	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	Singleton gestation nd 0%			Weight in offspring stratified by mother's 25(OH)D	0	X	X	0	X	X	

Abbreviations: X = factor adjusted for in analysis; O = factor not adjusted for.

Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report)

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 ⁵¹ Brooke 1980 ⁴⁷ [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 ^A	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 ^A	NS		
					Control	67		NA	49.5	49.4, 49.6					
Feliciano 1994 ⁴⁹ [8078115]	0–6 mo	Weight gain born in spring, N. China ^B	1°	6 mo	Vit D 400 IU	12	g	nd	3745	2613, 4877	-463	-1852, 926 ^A	NS	C	
					Vit D 200 IU	13		nd	5296	4718, 5874	1088	96, 2080 ^A	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 ^A	NS		
					Vit D 200 IU	13		nd	19	18.1, 19.9	-0.3	-2.2, 1.6 ^A	NS		
					Vit D 100 IU	15		nd	19.3	17.6, 21.0					
El-Hajj 2006 ⁴⁸ [16278262]	9–18 y female, premenarche	Height	2°	1 y	Vit D ₃ 2000 IU	nd, ≤34 total	%	nd	5.60%	~4.8, 6.4 ^C	~1.8%	~0.6, 3.0 ^A	0.07	C	
					Vit D ₃ 200 IU			nd	5.00%	~4.2, 5.8 ^C	~1.2%	~-0.01, 2.4 ^A			
					Placebo			nd	3.80%	~0.9, 6.7 ^C					
		Weight	2°	1 y	Vit D ₃ 2000 IU	nd, ≤34 total	%	nd	18.40%	~14.7, 22.1 ^C	~3.5%	~-1.3, 8.3 ^A	0.25		
					Vit D ₃ 200 IU			nd	15.30%	~12.5, 18.1 ^C	~0.4	-3.7, 4.5 ^A			
					Placebo			nd	14.90%	~11.8, 18.0 ^C					

Table 6 Vitamin D and growth outcomes: Results of RCTs (updated from original report) (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
Wagner 2006 ⁵² [17661565]	Lactating mothers & infant	Infant weight ^C	1°	7 mo	Mother (400) +infant (300)	10	g	NA	Final 7600	7100, 8100	Diff -800	-2300, 700 ^A	0.3	C
					Mother (6400) +infant (0)	9		NA	8400	7700, 9100				
	0–6 mo; 7 mo– 2 y	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 ^A	0.06	
					Mother (6400) +infant (0)	9		NA	69.3	67.4, 71.2				
Marya 1988 ⁵⁰ India [3243609]	Pregnant women & infant 0–6 mo	Birth weight	1°	Delivery	Vit D 1.2 mil IU total	100	g	NA	Final 2990	2920, 3060	Diff 190	90, 290 ^A	<0.001	C
					No supplement	100		NA	2800	2730, 2870				
		Birth length	2°		Vit D 1.2 mil IU total	100	cm	NA	Final 50.06	49.7, 50.4	Diff 1.6	1.1, 2.1 ^A	<0.001	
					No supplement	100		NA	48.45	48.1, 48.8				
Marya 1981 ⁵⁴ [7239350] ^E	Pregnant women & infant 0–6 mo	Birth weight	2°	Delivery	Vit D 1.2 mil IU total	20	g	NA	Final 3140	2940, 3340	Diff 410	166, 654 ^A	0.001	C
					Vit D 1200 IU + 375 mg Ca (3 rd trimester)	25	g	NA	Final 2890	2760, 3020	Diff 160	0, 320 ^A	0.05	
					No supplement	75		NA	2730	2650, 2810				
Mallet 1986 ⁵³ France (48° 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)					

Table 6 Vitamin D and growth outcomes: Results of RCTs (updated from original report) (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
NEW Studies														
Hollis 2011 ¹	Pregnant or lactating women	Birth weight	2°	Delivery	Vit D 4000 IU	117	g	NR	Final 3284.6	3175.2, 3394.0	+62.8	-103.4, 229.0	0.23	A
					Vit D 2000 IU	122			Final 3360.1	3255.2, 3465.0	+138.3	-24.4, 301.0		
					Vit D 400 IU	111			Final 3221.8	3094.9, 3348.8				
Kalra 2012 ⁴³	Pregnant or lactating women between 12–24 weeks gestation	Birth weight	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	kg	NR	Final 3.03	1.71, 4.35	-0.05	-1.92, 1.82	0.96	C
					1500 mg cholecalciferol (one dose 2nd trimester)	36	kg		Final 3.08	1.71, 4.45				
		Length at birth	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	cm	NR	Final 50.1	49.8, 50.4	-0.2	-0.6, 0.2	0.35	
					1500 mg cholecalciferol (one dose 2nd trimester)	36	cm		Final 50.3	50.0, 50.6				
Roth 2013 ⁴⁴		Birth weight	2°	Delivery	35000 IU Vit D ³ 3rd trimester	73	g	NR	Final 2802	2675, 2929	+14	-138, 166	0.86	A
					Placebo	74	g		Final 2788	2700, 2876				
		Length at birth	2°	Delivery	35000 IU Vit D ³ 3rd trimester	73	cm	NR	Final 48.2	47.6, 48.8	+0.2	-0.5, 0.9	0.55	
					Placebo	74	cm		Final 48	47.5, 48.5				
Wagner 2013 ⁴²		neonatal birth weight	1°		2000 IU vit D ³	201	g	NR	Final 3382	sd=759	+149	-21, 319	0.09	B
					4000 IU vit D ³	193			Final 3231	sd=632	-2	-154, 150		
					control	110			Final 3233	sd=668				

Note: Outcomes cells are shaded for the Control rows.

^AEstimated from available data.

^BSee Table 1 in original paper for complete results stratified by North vs. South China and birth in spring vs. fall.

^CSee Table 3 in original paper for results on 1 mo and 4 mo.

^DEstimated from number of mothers; number of infants not reported.

^EThis 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 (updated from original report)

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 ⁵⁶ 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		

Table 7 Vitamin D and growth outcomes: Results of cohort studies (updated from original report) (continued)

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
Gale 2008 ⁵⁵ 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	3.4	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	0.1	
				30–50	nd	29.4	1.21		
				50–75	nd	30	1.2		
				>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	2.6		
				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		

Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report) (continued)

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
NEW Studies									
Burris 2012 ⁴⁵	Pregnant or lactating women	Birth weight	Delivery	<25				ND	
				25–50					
				50–75					
				≥75					
Gernand 2013 ⁴⁶	singleton gestation	Birth weight	Delivery	<37.5				0.014	
				≥37.5					

Vitamin D and Cardiovascular Disease

Synopsis

One qualified systematic review of prospective studies identified for the current report found a significant association between low serum 25(OH)D concentrations and a number of clinical cardiovascular outcomes, including total cardiovascular disease, coronary heart disease, cardiovascular disease mortality, and stroke. No RCTs identified for the current report evaluated the effects of vitamin D on clinical cardiovascular disease outcomes. Observational studies identified for the current report found mixed associations between 25(OH)D and total cardiovascular events, cardiovascular death, myocardial infarction, stroke, and fatal stroke. Significant associations were found between progressively lower 25(OH)D concentration and increased risk for 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.

For the original report, 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 D₃ 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, and 11a-b; Figures 6a-h)

Total Cardiovascular Events (Figure 6a, b, e, and h)

One high-quality systematic review⁵⁷ that included 17 studies, 16 of which were included in the original report or the current report (the remaining study was excluded from the current report) found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.

Six prospective cohort studies evaluated the association between serum 25(OH)D concentrations and the incidence of total cardiovascular events, ranging from 4.4 years to 14.4 years followup. Three of these studies found no significant association between levels of serum 25(OH)D and risk for a cardiovascular event (two rated A, one rated B).⁵⁸⁻⁶⁰ One study, the German MONICA/KORA cohort study, with a mean followup of 11 years, found significantly decreased risks of total cardiovascular events for both men and women, with a larger effect in women (rated A).⁶¹ Another study, the U.S. MESA study, found an association of serum 25(OH)D with decreased risk of CHD among Caucasians and Chinese

participants but not among Black or Hispanic participants (rated A).⁶² The German ESTHER cohort study found that serum 25(OH)D concentrations of less than 75nmol/L were associated with an increased risk for all cardiovascular events (rated B).⁶³

Two nested case-control studies were identified. One nested case-control study within the Tehran Lipid and Glucose Study with 5.7 years followup found a significantly increased risk for total cardiovascular events for individuals in the lowest tertile of 25(OH)D concentrations compared with the two higher tertiles (rated B).⁶⁴ A study nested within the multi-country EPIC study found no association of serum 25(OH)D with total CV events in the fully adjusted model (rated A).⁶⁵

In the original report, total cardiovascular events were evaluated by an RCT,⁶⁶ the Framingham Offspring Study (FOS),⁶⁷ and a nested case-control study derived from the Health Professionals Followup Study (HPFS).⁶⁸ 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 D₃ 100,000 IU every 4 months or placebo.⁶⁶ 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 and those taking 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 range of 41 to 77 years).⁶⁷ 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.⁶⁸ 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% CI 1.1, 2.3), those with 25(OH)D 37.5 to 56 nmol/L had an RR of 1.4 (95% CI 0.96, 2.1), and those with 25(OH)D below 37.5 nmol/L had an RR of 2.1 (95% CI 1.2, 3.5).

Cardiovascular Death (Figures 6c and 6d)

Sixteen prospective studies and one nested case control study that examined the association between serum 25(OH)D and risk for cardiovascular death (including fatal myocardial infarction, sudden cardiac death, and coronary disease death) were identified for the current report. Seven prospective cohort studies (reported in eight articles) and the nested case control studies, with followups ranging from 7.3 to 29 years (one study did not report length of followup and one, an analysis of NHANES data, reported follow up in person years), observed an increased risk for cardiovascular death for those with the lowest serum 25(OH)D concentrations compared with the highest (three rated A, six rated B).^{63,69-76}

The study by Eaton, which followed a subsample of the Women's Health Initiative participants, found an association among women with normal waist to hip ratios but not among women with abdominal obesity (rated A).⁷⁰

The study by Signorello observed the association among both African American and non-African American participants (rated A).⁷⁴ A study by Fiscella of 15,363 adult participants in NHANES assessed differences between African Americans and whites and found a higher risk for cardiovascular death among blacks than whites that disappeared when adjusted for the lower serum 25(OH)D levels in blacks (rated A).⁷¹

The Whitehall study, reported by Tomson, observed a strong inverse association among elderly men between serum 25(OH)D and risk for cardiovascular death, at a median of 13 years' followup (rated B).⁷⁵ The ESTHER study reported a strong inverse association among men and women at two followup times (4.5 and 9.2 years)(both rated B).^{63,76}

The remaining 9 cohort studies, including the Octabaix 3-Year Followup study of the oldest old,⁷⁷ found no association between serum 25(OH)D concentrations and risk for cardiovascular death (four A, five B).^{58,78-84}

In the original report, the British RCT of vitamin D₃ 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.⁶⁶ Fewer people taking vitamin D₃ supplements had cardiovascular deaths (RR = 0.84), but this finding was not statistically significant (95% 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.⁸⁵ During almost 9 years of follow up, 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 (Figure 6a and b)

Three prospective cohort studies (reported in two articles) identified for the current report assessed the association between serum 25(OH)D concentrations and incident ischemic heart disease. These studies, one with a 10-year follow up and one with a 29-year follow up, found no significant difference in risk for nonfatal ischemic heart disease across four quartiles of serum 25(OH)D concentrations (both rated B).^{69,86}

The RCT evaluated total ischemic heart disease.⁶⁶ In this elderly British population, 17% had an ischemic heart disease event; no effect of vitamin D₃ supplementation was found. Similar results were found in subgroups of men and women.

Ischemic Heart Disease Death (Figure 6c and d)

The pooled results of two population-based studies reported in an article identified for the current report observed an association of serum 25(OH)D with death from ischemic heart disease (rated B).⁸⁶

An RCT identified for the original report evaluated total ischemic heart disease death as a primary outcome.⁶⁶ In the trial, 3.4% had an ischemic heart disease event; no effect of vitamin D₃ supplementation was found (RR = 0.84 [95% CI 0.56, 1.27]). Similar results were found in subgroups of men and women.

Myocardial Infarction (Figure 6e)

Five prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentration and risk for myocardial infarction. Four of the studies found no association (two rated A, two rated B).^{58,69,87,88} A nested case control study within the EPIC study with a mean follow up time of 7.6 years found an association between serum 25(OH)D and myocardial infarction when the outcomes were adjusted only for sex and BMI but no association with a model that adjusted for various lifestyle factors as well (rated A).⁶⁵ One cohort study that followed 2,312 older adults with no history of disease at baseline for 14 years found, after adjustment, that each 25nmol/L decrease in 25-OHD concentration was associated with a 25 percent greater (95% CI: 8% to 44% greater) relative hazard of myocardial infarction.⁸¹

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).⁸⁹ During 10 years of follow up, 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 (Figure 6f)

Seven prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentration and risk for stroke or transient ischemic attack. Three of the studies (followup ranging from 17 to 29 years) found a significantly increased risk for stroke or TIA for those with the lowest or lower serum 25(OH)D concentrations compared with those with the highest or higher concentrations, respectively (two rated B, one rated A),^{69,88,90} although for the women in the Nurses' Health Study,⁹⁰ the difference was relatively small. The remaining four studies, with followup of 5 to 13 years, found no difference (two rated A, two rated B).^{58,63,86,91}

One nested case control study within the EPIC population study, which had a followup of 7.6 years, reported a small j-shaped association of serum 25(OH)D with risk for stroke (rated A).⁶⁵

The RCT identified for the original report evaluated total cerebrovascular disease.⁶⁶ In this elderly British population, 7.7% had a cerebrovascular event; no effect of vitamin D₃ 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 follow up, 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 (Figure 6g)

Three prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentrations and risk for fatal stroke or cerebrovascular death.^{63,82,83} One study, with a median followup of 27 years, found an increased risk for the lowest quintile of 25(OH)D concentration compared with the highest (rated A).⁸² The other two studies, with mean followup of 9 and 24 years, found no significant association between serum 25(OH)D concentration and risk for fatal stroke or cerebrovascular death for either men or women both rated B).^{63,83}

The RCT identified for the original report evaluated cerebrovascular disease death as a primary outcome.⁶⁶ In the trial, 2.0% had a fatal stroke; no effect of vitamin D₃ supplementation was found. Similar results were found in subgroups of men and women.

Findings per Vitamin D Concentration

The RCT identified in the original study compared vitamin D₃ 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).⁶⁷ 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.⁸⁹

Findings per Age and Sex

For the observational studies identified for the current report, differences were similar among men and women.

The single RCT identified for the original report 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 **in the original report; an analysis of a larger population identified for the current report found an association, as did a European population-based study.**
- **≥71 y**
A number of new studies identified for the current report included a predominance of participants within this age group. Vitamin D supplementation and exposure were not consistently associated with cardiovascular outcomes in these studies. The majority of participants in the British RCT **identified for the original report** included men and women within this age group. Vitamin D supplementation was not found to have an effect on cardiovascular outcomes. Among the cohort studies, only the small Finnish study adequately evaluated people within this life stage. No significant associations were found between serum 25(OH)D or 1,25(OH)₂D concentrations and either myocardial infarction or stroke, however, the absolute concentrations were not reported.
- **Postmenopause**
In the original report, only the RCT provided data on a subgroup that included only postmenopausal women: No effect of vitamin D₃ supplementation was found. **For the current report, a post hoc assessment of a sample of WHI participants found an increased risk for cardiovascular death with decreasing serum 25(OH)D among normal weight postmenopausal women but not women with abdominal obesity.**⁷⁰
- **Pregnant & lactating women**
Not reviewed

Table 8. Vitamin D and cardiovascular outcomes: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 2003 ⁶⁶ Ipswich, UK (52°N) [12609940]	<ul style="list-style-type: none"> • 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 [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 2003 ⁶⁶ [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					

Note: Outcomes cells are shaded for the Control rows.
Similar results for subgroups of men and women

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report)

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 ⁶⁷ Framingham Offspring Framingham, MA (mostly) (42°N) [18180395]	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	No CVD 59 (9) 45	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (DiaSorin)	Outcome stratified by 2 or 3 categories	X ^A	X	X	X	X ^A	X	CVD event
Giovannucci 2008 ⁶⁸ HPFS US (various) [18541825]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	No CVD 64 (40-75) 100	<ul style="list-style-type: none">• 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 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 45 (≥20) 46	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (DiaSorin)	Outcome stratified by 4 categories	X	X	X	X	X	X	CVD death
Marniemi 2005 ⁸⁹ Turku, Finland (60°N) [15955467]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 79 (65-99) 48	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Incstar)	Outcome stratified by tertiles		X				X	MI Stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

				Confounders/Effect Modifiers Adjusted							
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Specific CVD Outcomes
New Studies:											
Bolland, 2010 ⁵⁸ New Zealand	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy Post-menopausal 74 (SD 4.2) 0%		Outcome stratified by 2 categories		X	X	X		X	MI Stroke MI, Stroke, or sudden death TIA Congestive heart failure Death
Brondum-Jacobsen, 2012 ⁶⁹ Copenhagen, Denmark	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	nd 57 (49–66) 44%		Outcome stratified by 4 categories		X	X	X	X	X	Nonfatal ischemic heart disease Nonfatal MI Fatal ischemic heart disease/MI
Brondum-Jacobsen, 2013 ⁹² Copenhagen, Denmark	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	nd 56 (48–65) 44%		Outcome stratified by 4 categories		X	X	X	X	X	Ischemic stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
deBoer, 2012 ⁸⁷ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 74 (SD 4.6) 30%	Outcome stratified by 2 categories		X	X			X	MI
Deo, 2011 ⁷⁸ Cardiovascular Health Study US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 74 (SD 4) 30%	Outcome stratified by 2 categories		X	X	X	X	X	Sudden Cardiac Death
Eaton, 2011 ⁷⁰ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 65.1 (7.6) 0%	Outcome stratified by 4 categories			X	X	X	X	Cardiovascular Disease Mortality
Fiscella, 2010 ⁷¹ NHANES-III nd	<ul style="list-style-type: none"> • Health status • Mean age, y • Male (%) 	nd 43.64 48%	Outcome stratified by 2 or 4 categories		X	X	X	X	X	Cardiovascular Death

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Ginde, 2009 ⁷² US (various)	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y 73 (0.2) • Male (%) 44% 		Outcome stratified by 5 categories		X	X	X	X	X	Cardiovascular Death
Hutchinson, 2010 ⁷⁹ Tromso Tromso, Norway	<ul style="list-style-type: none"> • Health Status nd • Mean age (SD), y nd • Male (%) nd 		Outcome stratified by 4 categories		X	X	X		X	CVD Mortality
Jassal, 2010 ⁸⁰ San Diego, CA	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y 74 (SD 10) • Male (%) 38% 		Outcome stratified by 2 categories				X			Cardiovascular Mortality
Karakas, 2013 ⁶¹ MONICA/KORA Augsburg case-cohort study	<ul style="list-style-type: none"> • Health status Healthy • Mean age (SD), y 51.9 (SD 0.42) • Male (%) 75.5% 	Range: 35–74	Outcome stratified by 3 categories		X			X		Coronary Heart Disease

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Kestenbaum, 2011 ⁸¹ CHS US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 73 (SD 4) 42%	Outcome stratified by 4 categories							Cardiovascular Mortality Incident heart mortality Incident myocardial infarction
Kilkinen, 2009 ⁸² Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 49.4 (SD 13.6) 45.3%	Outcomes stratified by 5 categories		X		X			Cardiovascular Death Cerebrovascular Death Coronary Disease Death
Lin, 2012 ⁸³ Linxian, China	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, Hypertension 27% 56.5 (SD 7.9) 55%	Outcome stratified by 3 categories		X	X	X		X	Cerebrovascular Death Cardiovascular Death
Messenger 2012 ⁵⁹ MrOS US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 76.1 (SD 5.6) 100%	Outcome stratified by 4 categories		X					Cardiovascular disease (CHD & CVA)

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Michaelsson 2010 ⁸⁴ Uppsala, Sweden	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	More than 1/3 being treated for hypertension 71 (SD 0.6) 100%	Outcome stratified by 3 categories	X	X	X	X	X	X	Cardiovascular mortality
Prentice 2013 ² WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Post-menopausal 50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5% 0%	Outcome stratified by 2 categories	X	X					MI Coronary heart disease Total heart disease Stroke Total cardiovascular disease
Schierbeck, 2012 ⁸⁸ Danish Osteoporosis Prevention Study Denmark	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Post-menopausal 50 (SD 2.8) 0%	Outcome stratified by 2 categories		X	X			X	Heart failure Myocardial Infarction Stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Signorello, 2010 ⁷⁴ US	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y nd (nd) • Male (%) nd 		Outcome stratified by 4 categories			X			X	Circulatory disease death
Sun, 2012 ⁹⁰ Nurses' Health Study US (multiple)	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y 60.8 (5.9) • Male (%) 0% 		Outcome stratified by 3 categories							Ischemic stroke
Welsh 2012 ⁶⁰ MIDSPAN Family Study UK	<ul style="list-style-type: none"> • Health status Vitamin D deficient/depleted Vitamin D not deficient • Mean age (SD), y 45.2 (6.2) • Male (%) 46% 		Outcome stratified by 4 categories	X	X	X	X	X	X	Cardiovascular event
Formiga 2014 ⁷⁷ Octabaix Spain	<ul style="list-style-type: none"> • Health status Oldest old • Mean age 85 • Male (%) 39.4% 		Outcome stratified by 4 categories		X		X			Cardiovascular mortality

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Tomson 2013 ⁷⁵ Whitehall study London, UK	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%	Outcome stratified by 4 categories			X	X		X	Death, ischemic heart disease Death, stroke Death, other vascular Death, all vascular
Skaaby 2013 ⁸⁶ Monica10 and Inter99 Denmark	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR Monica 10: 55.4 (41–72.8) Inter99: 46.1(29.7–61.3) 50.2%	Outcome stratified by 4 categories		X		X	X	X	Ischemic Heart Disease Stroke
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 62 (SD 6.5) 43.8%	Outcome stratified by 3 categories		X		X	X	X	CVD mortality
Robinson-Cohen 2013 ⁶² MESA US	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 63.3 (SD 10.2) 47%	Outcome stratified by 4 categories	X	X	X	X		X	Incident coronary heart disease events

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

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	
Perna 2013 ⁶³ ESTHER Saarland, Germany	<ul style="list-style-type: none">• Health status• Mean age• Male (%)	46.3% hypertension		Outcome stratified by 4 categories	X	X	X	X	X	X	Total CVD
		NR (range 50–74)									Nonfatal CVD
		40.7%									Fatal CVD
											Total CHD
											Nonfatal CHD
											Fatal CHD
											Total Stroke
											Nonfatal Stroke
Kuhn 2013 ⁶⁵ EPIC-Germany Heidelberg, Potsdam	<ul style="list-style-type: none">• Health status• Mean age• Male (%)	NR		Outcome stratified by 4 categories		X	X		X	X	Myocardial Infarction
		NR									Stroke
											CVD as composite endpoint
Brodin 2013 ⁹¹ Tromso study Norway	<ul style="list-style-type: none">• Health status• Mean age• Male (%)	NR		Outcome stratified by 5 categories		X	X			X	Total Venous Thromboembolism
		62 (SD 10)									
		37%									

^ANot in 3-category analysis

^BCase-control study

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report)

Author Year	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
[PMID]											
CVD Events											
Both Sexes											
Wang 2008 ⁶⁷	Mean (SD) 59 (9), Both	CVD event (120/1739; 0.069)	5.4 y	25(OH)D	<37.5	50	481	1.7	1.08, 2.67*	0.02 ^A	A
					≥37.5	70	1258	1	Reference		
Framingham Offspring					<25	nd	nd	1.8	1.05, 3.08*	0.01	C
					25–37.5	nd	nd	1.53	1.00, 2.36*		
[18180395]					≥37.5	70	1258	1	Reference		
Men											
Giovannucci 2008 ⁶⁸	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		
HPFS					56.25–75	165	464	1.6	1.10, 2.32		
[18541825]					>75	70	277	1	Reference		
CVD Death											
Both Sexes											
Melamed 2008 ⁸⁵	≥20 y, Both	CVD death (777/13,331; 0.058)	8.7 y	25(OH)D	<44.5	nd	nd	1.2	0.87, 1.64	nd	C
					44.5–60.75	nd	nd	0.88	0.69, 1.14		
NHANES III					60.75–80.25	nd	nd	0.83	0.65, 1.07		
					>80.25	nd	nd	1	Reference		
[18695076]											

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Myocardial Infarction											
Both Sexes											
Marniemi 2005 ⁸⁹ [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) ₂ D	nd	nd	~252	1	Reference	nd	
					nd	nd	~252	1.05	0.68, 1.62		
					nd	nd	~252	0.82	0.52, 1.30		
Stroke											
Both Sexes											
Marniemi 2005 ⁸⁹ [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	0.51, 1.94		
				1,25(OH) ₂ D	nd	nd	~252	1	Reference	nd	
					nd	nd	~252	0.63	0.37, 1.09		
					nd	nd	~252	0.41	0.22, 0.77*		
NEW Studies											
Bolland 2010 ⁵⁸ New Zealand	Primary–MI	5 y	25(OH)D	<50 nmol/L	31	736	1.20	0.7, 2.2	0.52	A	
				≥50 nmol/L	21	735	1.00	Reference			
	Primary–Stroke	5 y	25(OH)D	<50 nmol/L	37	736	1.40	0.8, 2.5	0.20		
				≥50 nmol/L	22	735	1.00	Reference			
	Primary–MI, Stroke, or sudden death	5 y	25(OH)D	<50 nmol/L	65	736	1.20	0.8, 1.8	0.34		
				≥50 nmol/L	45	735	1.00	Reference			
	Primary–TIA	5 y	25(OH)D	<50 nmol/L	24	736	1.10	0.6, 2.0	0.76		
				≥50 nmol/L	21	735	1.00	Reference			
	Primary–Congestive heart failure	5 y	25(OH)D	<50 nmol/L	12	736	1.00	0.4, 2.4	0.97		
				≥50 nmol/L	10	735	1.00	Reference			
	Primary–Death	5 y	25(OH)D	<50 nmol/L	34	736	0.90	0.5, 1.6	0.73		
				≥50 nmol/L	29	735	1.00	1.00			

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Brondum- Jacobsen 2012 ⁶⁹	51–70 years	Primary–Nonfatal ischemic heart disease	29 y	25(OH)D	<25.0 nmol/L	381	2,553	1.08	0.85, 1.37	0.1	B
					25.0–49.9 nmol/L	648	4,068	1.01	0.81, 1.26		
					50.0–74.9 nmol/L	391	2,470	0.91	0.72, 1.15		
					≥75.0 nmol/L	158	1,079	1.00	Reference		
					<25.0 nmol/L	224	2,553	1.17	0.83, 1.63	0.4	
		Primary–Nonfatal MI	29 y	25(OH)D	25.0–49.9 nmol/L	350	4,068	0.97	0.71, 1.34		
					50.0–74.9 nmol/L	228	2,470	1.02	0.74, 1.42		
					≥75.0 nmol/L	89	1,079	1.00	Reference		
					<25.0 nmol/L	422	2,553	1.53	1.18, 1.98	<0.001	
		Primary–Fatal ischemic heart disease/MI	29 y	25(OH)D	25.0–49.9 nmol/L	627	4,068	1.23	0.96, 1.58		
					50.0–74.9 nmol/L	367	2,470	1.18	0.91, 1.54		
					≥75.0 nmol/L	106	1,079	1.00	Reference		
Brondum- Jacobsen 2013 ⁹²	51–70 years	Primary– Ischemic stroke	29 y	25(OH)D	<25.0 nmol/L	350	2,553	1.36	1.09, 1.70	<0.001	A
					25.0–49.9 nmol/L	504	4,068	1.10	0.89, 1.36		
					50.0–74.9 nmol/L	277	2,470	0.92	0.74, 1.16		
					≥75.0 nmol/L	125	1,079	1.00	Reference		
deBoer 2012 ⁸⁷		MI	11 y	25(OH)D	Normal level	154	1126	HR 1.00	Reference	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	67	495	HR 1.24	0.91–1.70		
Deo 2011 ⁷⁸	≥ 65 years	Primary–Sudden cardiac death	14 y (median)	25(OH)D	<50 nmol/L	31	715	1.47	0.88, 2.46	Not sig	A
					≥50 nmol/L	42	1,568	1.00	Reference		
Cardiovascular Health Study											

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Eaton 2011 ⁷⁰	Post- meno- pausal women 50–79 years	Cardiovascular disease mortality	10 y	25(OH)D	Quartile 1: 3.25– 36.50 nmol/L		608	HR 1.27	0.81, 1.99	0.33	A
					Quartile 2: 36.51–49.95 nmol/L		606	HR 1.14	0.74, 1.78		
					Quartile 3: 49.96–65.38 nmol/L		608	HR 1.16	0.75, 1.80		
					Quartile 4: 65.39–146.67 nmol/L		607	HR 1.00	Reference		
Fiscella 2010 ⁷¹ NHANES-III		Primary– Cardiovascular death	138,549 person years	25(OH)D	Q1: <45 nmol/L			1.00	Reference		A
					Q2: 45–62.25 nmol/L	933	15363	0.71	0.54, 0.94	NR	
					Q3: 62.5–79.75 nmol/L			0.65	0.53, 0.79	NR	
					Q4: >80 nmol/L			0.79	0.62, 1.01	NR	
Ginde 2009 ⁷²	>= 65 years	Cardiovascular death	7.3 y	25(OH)D	<25.0 nmol/L		115	2.36	1.17, 4.75	<0.05	B
					25.0–49.9 nmol/L		904	1.54	1.01, 2.34	<0.05	
					50.0–74.9 nmol/L	767	1296	1.26	0.85, 1.88	NS	
					75.0–99.9 nmol/L		775	1.20	0.79, 1.81	NS	
					≥100.0 nmol/L		318	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Hutchinson 2010 ⁷⁹	25–84 yrs				Quartile 1: mean=33.8 (sd=7.6)	106	1184	HR 1.08	0.79–1.48	NR	B
					Quartile 2: mean=46.7 (sd=6.0)	81	1187	HR 0.84	0.61–1.15		
					Quartile 3: mean=56.2 (sd=6.0)	62	1192	HR 0.71	0.51–1.01		
					Quartile 4: mean=72.3 (sd=13.2)	76	1188	HR 1.00	Reference		
					Quartile 1: mean=33.8 (sd=7.6)	45	597	HR 0.93	0.61–1.44	NR	
					Quartile 2: mean=46.7 (sd=6.0)	57	606	HR 1.10	0.73–1.67		
					Quartile 3: mean=56.2 (sd=6.0)	46	607	HR 1.04	0.67–1.60		
					Quartile 4: mean=72.3 (sd=13.2)	40	600	HR 1.00	Reference		
Jassal 2010 ⁸⁰		Primary–Cardiovascular mortality	10.4 y	25(OH)D	per SD increase in serum 25(OH)D	111	1073	1.07	0.86, 1.33	NS	A
					per SD increase in log of serum 1,25(OH)2D	111	1073	0.98	0.80, 1.21	NS	

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Karakas 2013 ⁶¹					54.14–153.92 nmol/L			0.84	0.52, 1.35	0.461	A
MONICA/KORA Augsburg case-cohort study	Men 35–74 years	Primary–Coronary heart disease	11 y	25(OH)D in men	35.05–54.13 nmol/L	225	964	0.66	0.43, 1.02		
					5.08–35.02 nmol/L			1.00	Reference		
	Women 35–74 years		11 y	25(OH)D in women	47.70–127.69 nmol/L	73	819	0.42	0.19, 0.93	0.028	
					33.16–47.69 nmol/L			0.67	0.35, 1.29		
					9.87–33.15 nmol/L			1.00	Reference		
Kestenbaum 2011 ⁸¹	>65 years	Primary–Cardiovascular mortality	14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	389	2312	1.06	0.94, 1.19	0.356	B
CHS	<37.5nmol/L				107	681	1.17	0.83, 1.67			
	37.5–75nmol/L				207	1247	1.01	0.78, 1.30			
	>75nmol/L				75	384	1.00	Reference			
	Primary–Incident heart failure		14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	504	2312	0.95	0.86, 1.05	0.303	
<37.5nmol/L					107	681	1.17	0.83, 1.67			
37.5–75nmol/L					207	1247	1.01	0.78, 1.30			
>75nmol/L					75	384	1.00	Reference			
	Primary–Incident myocardial infarction		14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	299	2312	1.25	1.08, 1.44	0.002	
<37.5nmol/L					88	681	1.40	0.93, 2.12			
37.5–75nmol/L					161	1247	1.20	0.90, 1.59			
>75nmol/L					50	384	1.00	Reference			

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Kilkinen 2009 ⁸²	≥ 30 years	Primary– Cardiovascular death	27.1 y (median)	25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	150	1253	0.76	0.61, 0.95	0.005	A
					M:48.0–61.0 nmol/l F:44.0– 55.0 nmol/l	171	1222	0.86	0.70, 1.06		
					M:38.0–47.0 nmol/l F:34.0– 43.0 nmol/l	164	1284	0.81	0.66, 1.00		
					M:29.0–37.0 nmol/l F:26.0– 33.0 nmol/l	194	1202	1.04	0.86, 1.26		
					M:5.0–28.0 nmol/l F:4.0– 25.0 nmol/l	254	1258	1.00	Reference		
		Primary– Cerebrovascular death	27.1 y (median)	25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	33	1253	0.48	0.31, 0.75	0.002	
					M:48.0–61.0 nmol/l F:44.0– 55.0 nmol/l	48	1222	0.69	0.48, 1.00		
					M:38.0–47.0 nmol/l F:34.0– 43.0 nmol/l	68	1284	0.97	0.70, 1.35		
					M:29.0–37.0 nmol/l F:26.0– 33.0 nmol/l	52	1202	0.80	0.57, 1.14		
					M:5.0–28.0 nmol/l F:4.0– 25.0 nmol/l	92	1258	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
		Primary–Coronary disease death	27.1 y (median)	25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	117	1253	0.91	0.70, 1.18	0.2	
					M:48.0–61.0 nmol/l F:44.0–55.0 nmol/l	123	1222	0.95	0.74, 1.22		
					M:38.0–47.0 nmol/l F:34.0–43.0 nmol/l	96	1284	0.73	0.56, 0.95		
					M:29.0–37.0 nmol/l F:26.0–33.0 nmol/l	142	1202	1.17	0.93, 1.48		
					M:5.0–28.0 nmol/l F:4.0–25.0 nmol/l	162	1258	1.00	Reference		
Lin 2012 ⁸³	Men 40–69 yrs	Cerebrovascular death	24 y	25(OH)D	continuous	279	1101	HR 1.05	0.98, 1.12	0.141	B
					25(OH)D	157	608	HR 1.04	0.96, 1.13	0.337	
	Women 40–69 yrs					122	493	HR 1.06	0.96, 1.17	0.277	
						200	1101	HR 0.98	0.91, 1.06	0.678	
	Men 40–69 yrs	cardiovascular death	24 y	25(OH)D	continuous	119	608	HR 0.94	0.85, 1.04	0.223	
					25(OH)D	81	493	HR 1.06	0.93, 1.20	0.399	
Women 40–69 yrs											
Messenger 2012 ⁵⁹	≥ 65 yrs	Primary–Cardiovascular disease(CHD & CVA)	4.4 y (median)	Dietary Vit D intake	<168.6 IU	107	3094	0.76	0.56, 1.04	0.29	A
168.6–437.8 IU	125				0.97	0.72, 1.30					
437.9–572.3 IU	108		0.85	0.63, 1.15							
>572.3 IU	132		1.00	Reference							
MrOS			4.4 y (median)	25(OH)D	12–50.25 nmol/L	39	204	1.18	0.69, 2.03	0.85	
					50.5–63nmol/L	33	203	1.11	0.65, 1.91		
					63.25–75 nmol/L	35	202	0.97	0.57, 1.64		
					75.25–138.5 nmol/L	33	204	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Michaelsson 2010 ⁸⁴	birth 1920–1924	cardiovascular mortality	12.7 y	25(OH)D	< 10th percentile (<46 nmol/L)	24	119	HR 1.53	0.97, 2.41		B
10th–90th percentile (46–93 nmol/L)					135	956	HR 1.00	Reference			
>90th percentile (>93 nmol/L)					18	119	HR 1.16	0.69, 1.93			
Prentice 2013 ² WHI		Primary–MI	7.2 y	25(OH)D	≥400IU/day	40	1,914	1.06	0.75, 1.51	0.38	A
		no supplementation			433	23,561	1.00	Reference			
	Primary–Coronary heart disease	≥400IU/day			50	1,914	0.74	0.58, 0.95	0.53		
		no supplementation			545	23,561	1.00	Reference			
	Primary–Total heart disease	≥400IU/day			132	1,914	0.96	0.79, 1.16	0.82		
		no supplementation			1602	23,561	1.00	Reference			
	Primary–Stroke	≥400IU/day			38	1,914	0.84	0.66, 1.07	0.47		
		no supplementation			471	23,561	1.00	Reference			
	Primary–Total cardiovascular disease	≥400IU/day			181	1,914	0.92	0.778, 1.09	0.81		
		no supplementation	2187	23,561	1.00	Reference					
Schierbeck 2012 ⁸⁸ Danish Osteoporosis Prevention Study		Primary–Heart failure	16 y	25(OH)D	<50 nmol/l	10	788	1.88	0.71, 5.01	0.206	B
		≥50 nmol/l			8	1225	1.00	Reference			
	Primary–Myocardial Infarction	<50 nmol/l			13	788	0.83	0.41, 1.67	0.597		
		≥50 nmol/l			22	1225	1.00	Reference			
	Primary–Stroke	<50 nmol/l			47	788	1.68	1.10, 2.56	0.017		
		≥50 nmol/l	42	1225	1.00	Reference					

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Study Name (PMID)											
Semba 2010 ⁹³					1st quartile: <26.25 nmol/L	NR	252	HR 2.11	1.22, 3.64		B
		all-cause mortality	6.5 yrs	25(OH)D	2nd quartile: 26.25–40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.25–64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		
					1st quartile: <26.25 nmol/L	NR	252	HR 2.23	0.95, 5.25		
		cardiovascular mortality			2nd quartile: 26.25–40.0 nmol/L	NR	254	HR 1.58	0.71, 3.53		
					3rd quartile: 40.25–64 nmol/L	NR	247	HR 2.11	1.01, 4.43		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Signorello 2010 ⁷⁴					Quartile 4: (>54.1 nmol/L)	41	109	1.00	Reference	0.01	A
African Americans		circulatory disease death	NR	25(OH)D	Quartile 3: (37.9–54.1 nmol/L)	76	162	1.67	0.95, 2.93		
					Quartile 2: (25.45–37.88 nmol/L)	116	225	1.78	1.05, 3.01		
					Quartile 1: <25.45 nmol/L)	144	258	2.53	1.44, 4.46		
non-African Americans		circulatory disease death	NR	25(OH)D	Quartile 4: (>54.1 nmol/L)	40	107	1.00	Reference	0.01	
					Quartile 3: (37.9–54.1 nmol/L)	38	84	1.09	0.51, 2.30		
					Quartile 2: (25.45–37.87 nmol/L)	37	56	3.66	1.50, 8.95		
					Quartile 1: <25.45 nmol/L)	39	61	3.25	1.33, 7.93		
Sun 2012 ⁹⁰		Primary— Ischemic stroke	17 y	25(OH)D	9.2–45.7 nmol/l	171	325	1.49	1.01, 2.18	0.04	A
Nurses' Health Study					45.8–65.4 nmol/l	160	314	1.26	0.89, 1.79		
					66.5–264.3 nmol/l	133	289	1.00	Reference		
Welsh 2012 ⁶⁰					per 1 SD increase in dietary Vit D intake-log scale	293	1492				B
MIDSPAN Family Study		Primary— Cardiovascular event	14.4 y (median)	Dietary Vit D intake	per 1 SD increase in 25(OH)D-log scale	293	1492	0.94	0.83, 1.08	NR	
				25(OH)D	<37.5 nmol/L	293	1492	1.07	0.94, 1.23	NR	
				25(OH)D	≥37.5 nmol/L	293	1492	1.00	0.77, 1.31	NR	
				25(OH)D	≥37.5 nmol/L	293	1492	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Tomson 2013 ⁷⁵ Whitehall study		Death, ischemic heart disease	13.1 yrs	25(OH)D	Doubling Concentration	659	5409	0.84	0.70, 1.02		B
		Death, stroke				378	5409	0.81	0.63, 1.03		
		Death, other vascular				321	5409	0.71	0.54, 0.93		
		Death, all vascular				1358	5409	0.80	0.70, 0.91		
Robinson-Cohen 2013 ⁶² MESA		incident coronary heart disease events	8.5 yrs	25(OH)D	<85.92	120	2131	1.32	0.95, 1.83	0.04	A
					85.92–124.58	134	2224	1.20	0.91, 1.58		
					≥124.58	107	2081	1.00	Reference		
					per 42.96 decrement	361	6436	1.15	1.01, 1.32		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year	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
Study Name (PMID)											
Perna 2013 ⁶³					< 30	171	1114	1.24	1.02, 1.50		
		total cvd	6.5 yrs	25(OH)D	30–<50	448	3430	1.14	0.99, 1.32		
					>=50	392	3165	1.00	Reference		
					per 25	1011	7709	0.95	0.89, 1.01		
					< 30	136	1114	1.17	0.94, 1.45		
		nonfatal cvd			30–<50	383	3430	1.15	0.98, 1.35		
					>=50	335	3165	1.00	Reference		
					per 25	854	7709	0.98	0.91, 1.05		
					< 30	40	1114	1.55	1.01, 2.37		
		fatal cvd			30–<50	71	3430	1.05	0.73, 1.49		
					>=50	65	3165	1.00	Reference		
					per 25	176	7709	0.89	0.66, 0.94		
					< 30	92	1114	1.32	1.02, 1.72		
		total chd			30–<50	236	3430	1.19	0.98, 1.45		
					>=50	208	3165	1.00	Reference		
					per 25	536	7709	0.92	0.84, 1.01		
					< 30	77	1114	1.28	0.97, 1.71		
		nonfatal chd			30–<50	204	3430	1.18	0.95, 1.46		
					>=50	179	3165	1.00	Reference		
					per 25	460	7709	0.96	0.88, 1.06		
					< 30	16	1114	1.53	0.80, 2.94		
		fatal chd			30–<50	32	3430	1.18	0.70, 1.99		
					>=50	31	3165	1.00	Reference		
					per 25	79	7709	0.7	0.54, 0.93		
					< 30	64	1114	1.31	0.95, 1.81		
		total stroke			30–<50	165	3430	1.2	0.94, 1.54		
					>=50	124	3165	1.00	Reference		
					per 25	353	7709	0.91	0.81, 1.02		
					< 30	55	1114	1.26	0.89, 1.77		
		nonfatal stroke			30–<50	146	3430	1.19	0.92, 1.55		
					>=50	112	3165	1.00	Reference		
					per 25	313	7709	0.91	0.81, 1.02		
					< 30	9	1114	1.86	0.74, 4.66		
		fatal stroke			30–<50	20	3430	1.44	0.68, 3.03		
					>=50	12	3165	1.00	Reference		
					per 25	41	7709	0.86	0.61, 1.23		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Schottker 2013 ⁷⁶ ESTHER		CVD mortality	9.5 yrs	25(OH)D	<30 30–50 >50	71 137 142	1439 4188 3927	1.29 0.94 1.00	0.94, 1.76 0.73, 1.21 Reference		B
Skaaby 2013 ⁸⁶ Monica10 and Inter99		ischemic heart disease	10 yrs	25(OH)D	per 10nmol/L Q1 Q2 Q3 Q4	478	8131	1.01 1.00 1.17 1.00 1.24	0.98, 1.05 Reference 0.91, 1.51 0.76, 1.31 0.95, 1.62	0.44 0.25	B
		stroke			per 10nmol/L Q1 Q2 Q3 Q4	316	8131	1.00 1.00 1.08 1.18 1.13	0.96, 1.05 Reference 0.79, 1.49 0.86, 1.63 0.80, 1.59	0.92 0.78	
Kuhn 2013 ⁶⁵ EPIC-Germany		Myocardial Infarction			Q4: median 66.5 Q3: median 50.5 Q2: median 40.4 Q1: median 28.9	118 117 158 166	533 533 533 533	1.00 0.95 1.24 1.43	Reference 0.70, 1.28 0.93, 1.66 1.07, 1.92	0.19	
		stroke	7.6 yrs	25(OH)D	Q4: median 66.6 Q3: median 50.5 Q2: median 40.4 Q1: median 28.9	111 101 102 157	533 533 533 533	1.00 0.86 0.83 1.37	Reference 0.63, 1.17 0.61, 1.12 1.02, 1.84	0.19	A
		CVD as composite endpoint			Q4: median 66.5 Q3: median 50.5 Q2: median 40.4 Q1: median 28.9	229 218 260 323	533 533 533 533	1.00 0.89 1.06 1.41	Reference 0.70, 1.14 0.83, 1.35 1.11, 1.79	0.12	

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (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
Brodin 2013 ⁹¹ Tromso study		total venous thromboembolis m	10.7 yrs	25(OH)D	<=44	50	1474	1.00	Reference	0.89	A
					45–56	58	1470	0.72	0.41, 1.30		
					57–69	46	1481	0.93	0.55, 1.50		
					>=70	47	1480	0.76	0.45, 1.28		
					per 1 sd decrease in serum 25ohd	201	5905	1.02	0.91, 1.22		
Formiga 2014 ⁷⁷ Octabaix		Cardiovascular mortality	2.8 yrs	25(OH)D	Q1: <34.94	6	71	1.04	0.33, 3.24	0.86	B
					Q2: 34.94–61.65	6	77	0.89	0.28, 2.80		
					Q3: 61.66–83.37	6	84	1.47	0.45, 4.58		
					Q4: >83.37	7	80	1.00	Reference		

*Statistically significant (P<0.05)

Table 11b. Vitamin D and cardiovascular outcomes: Results of nested case-control studies (new table)

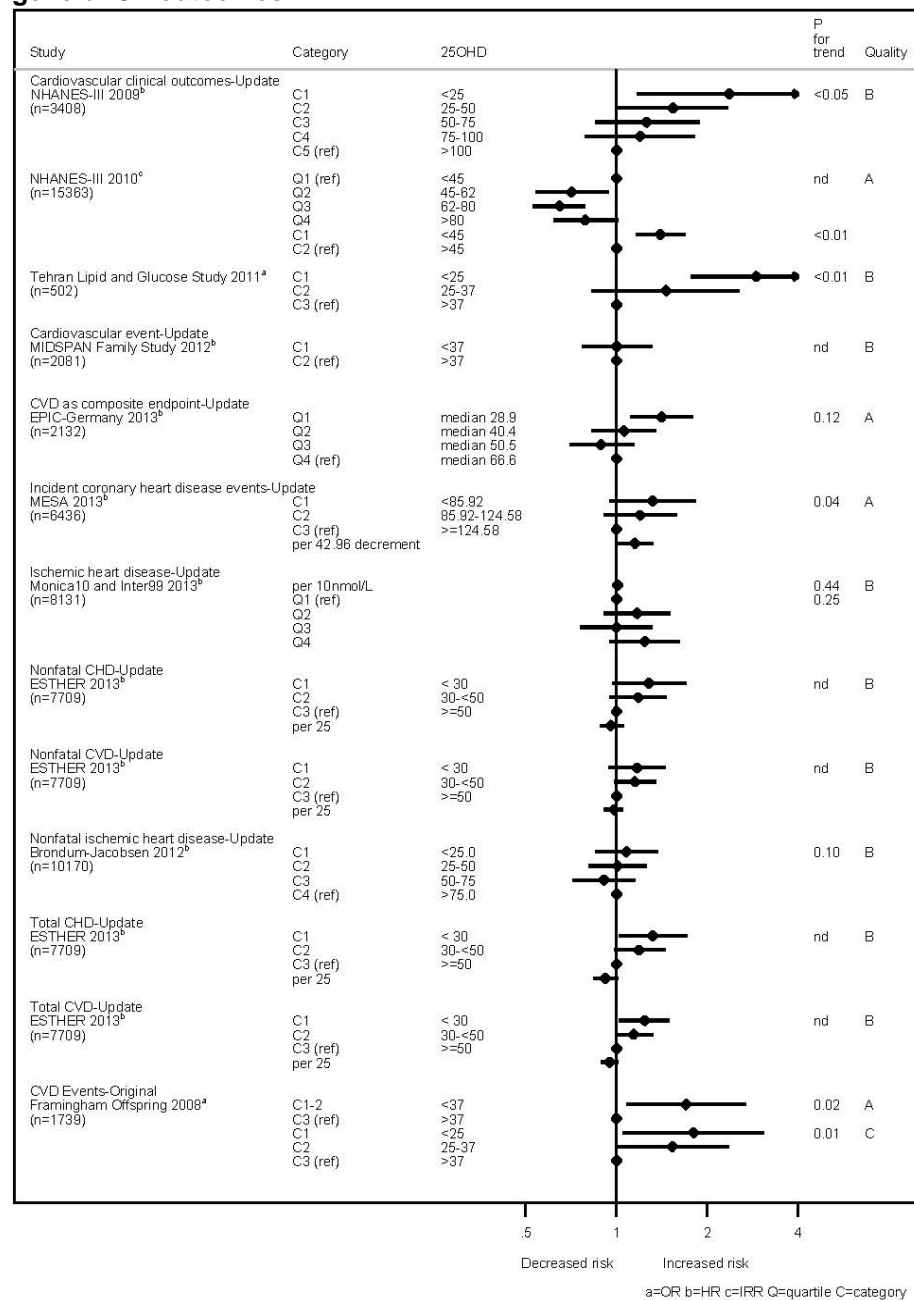
Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Hosseinpanah 2011 ⁶⁴ Tehran Lipid and Glucose Study (TLGS)	19–70 years	Primary– Cardiovascular disease	5.7 y	25(OH)D	<25.0 nmol/L	85	133	2.90	1.76, 4.67	<0.001	B
					25–37.48 nmol/L	86	173	1.46	0.83, 2.56	0.18	
					≥37.5 nmol/L	80	196	1.00	Reference		
Pilz 2009 ⁷³		cardiovascular mortality	6.2 y	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	12	152	5.38	2.02, 14.34	0.001	B
					2nd–4th quartiles (mean 25(OH)D 45.6– 78.9)	8	462	1.00	Reference		

^AMultivariable 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.

^BAdjusted 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.

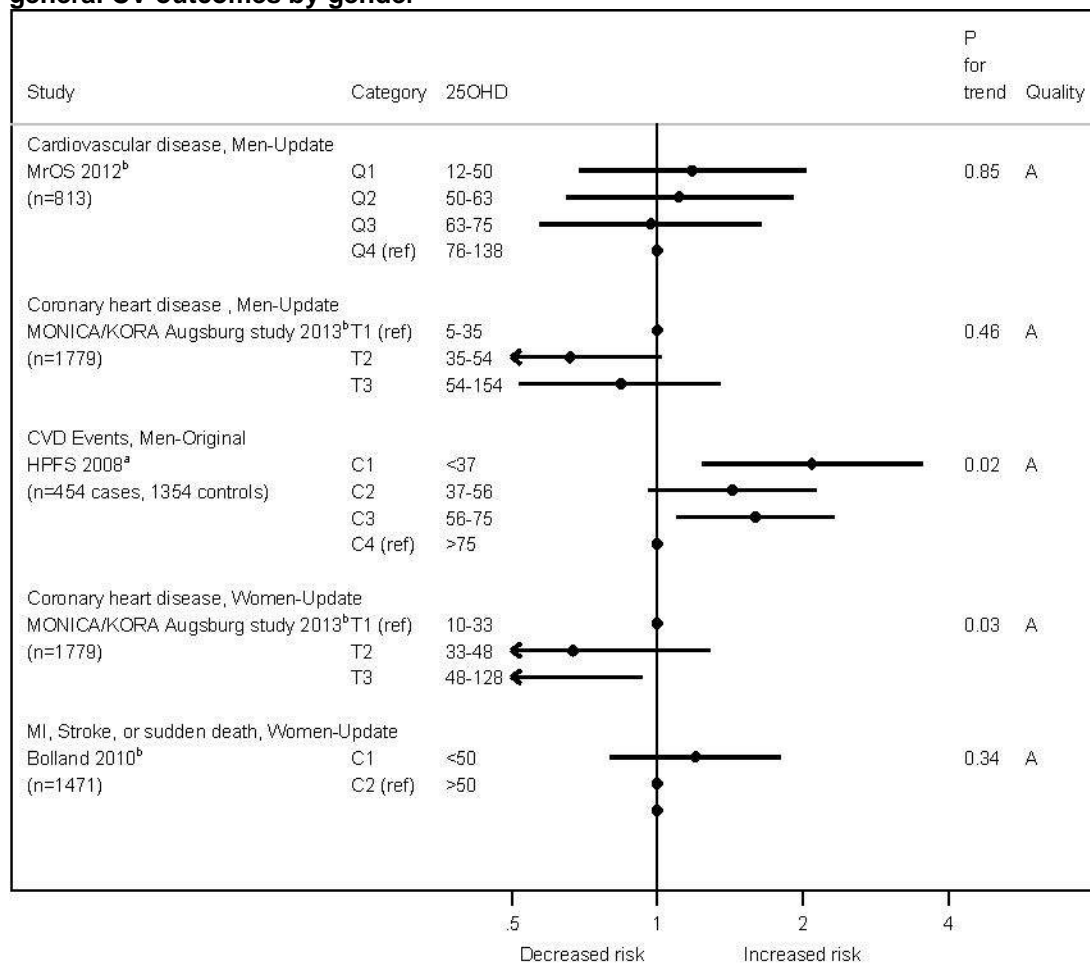
^CIn a subgroup analysis of participants on no cholesterol lowering drugs at baseline, comparing the highest serum 25(OH)D concentration category (>75 nmol/L) to the lowest (≤37.5 nmol/L), adjusted RR=2.30 (1.33, 3.97).

Figure 6a. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes



Abbreviations: CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer; ESTHER = EStrogen and THromboEmbolic Risk Study; MESA = Multi-ethnic Study of Atherosclerosis; NHANES = National Health and Nutrition Examination Study

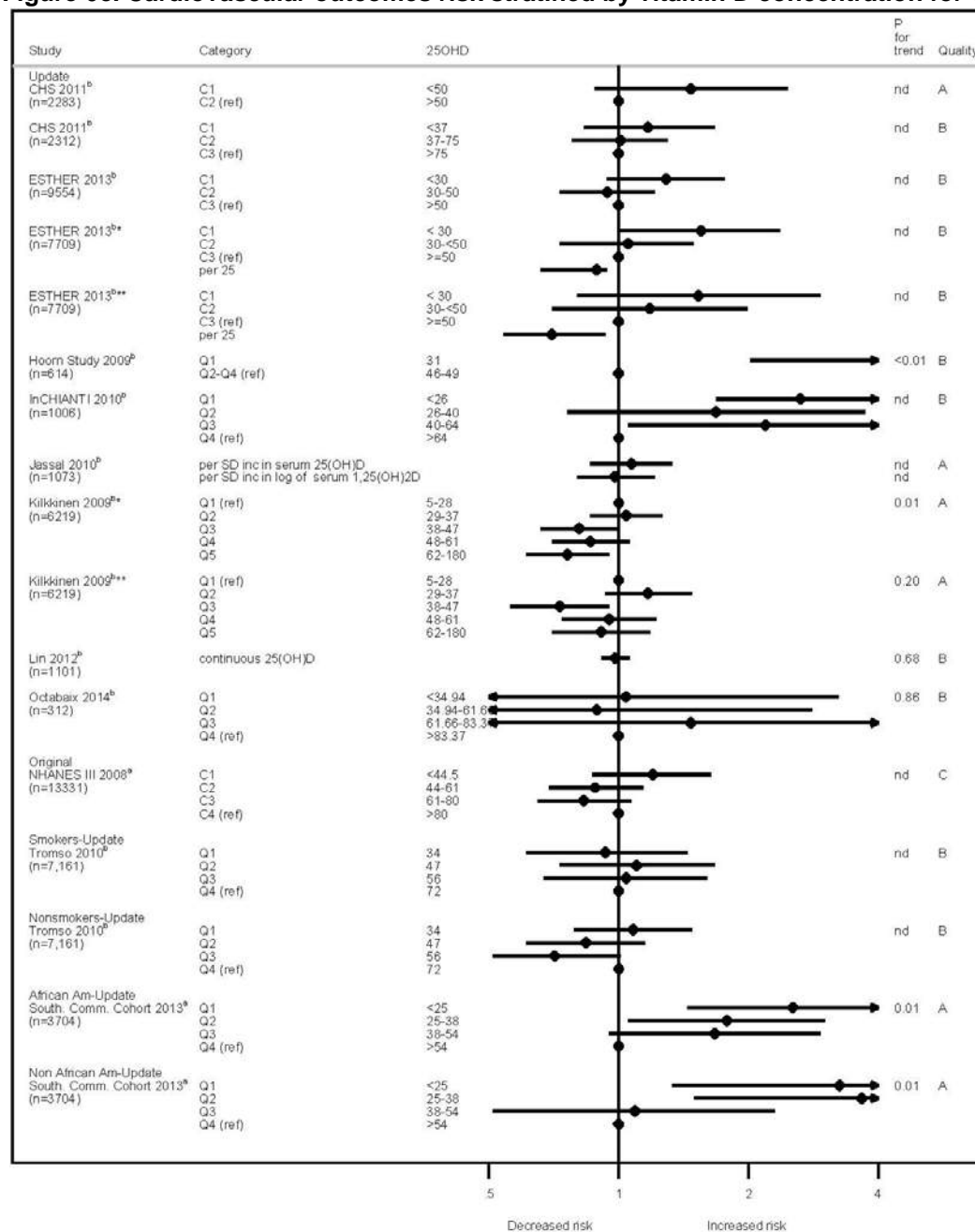
Figure 6b. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes by gender



a=OR b=HR T=tertile Q=quartile C=category

Abbreviations: MONICA = Multinational MONItoring of trends and determinants in CArdiovascular disease Study; KORA = Cooperative Health Research in the Region Augsburg; HPFS = Health Professionals Follow-Up Study

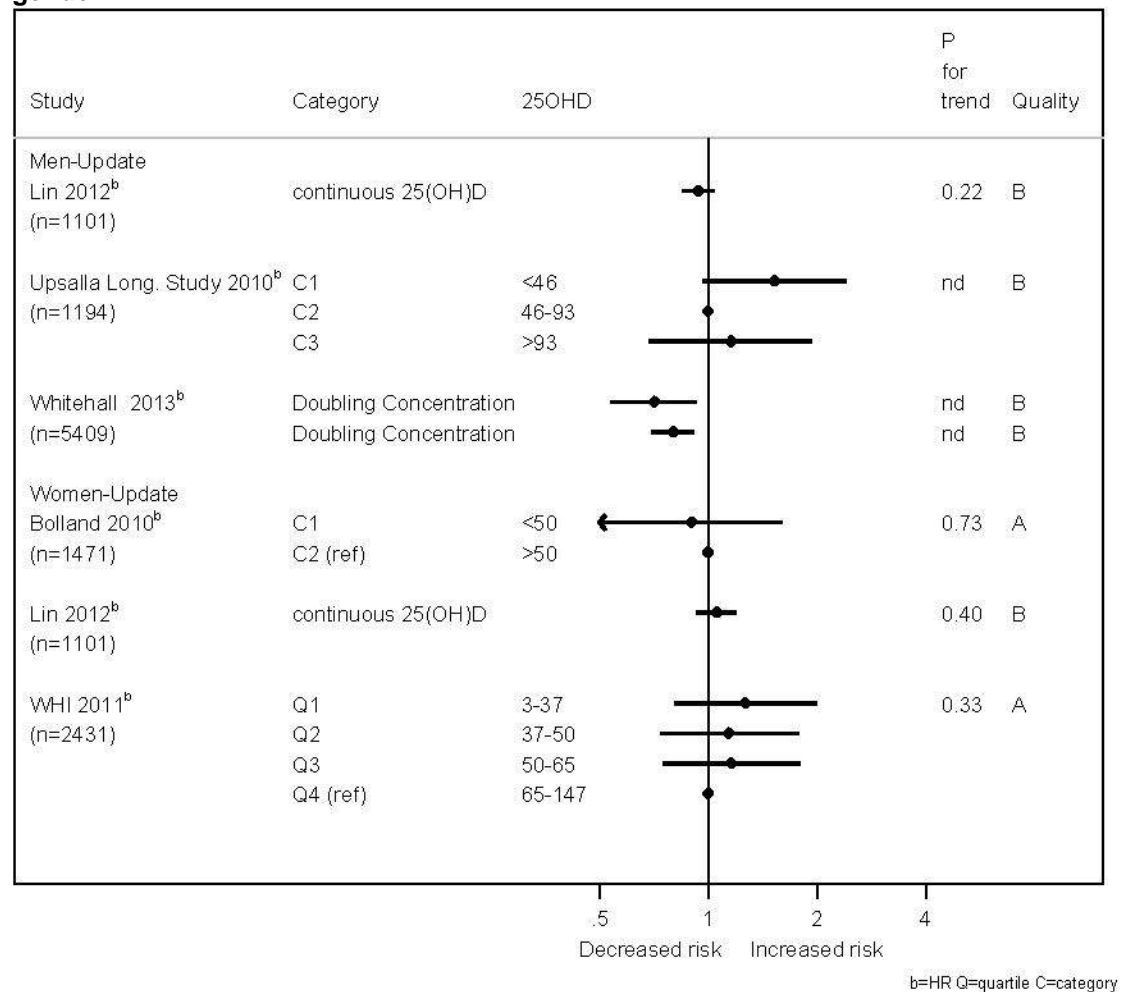
Figure 6c. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality



a=OR b=HR Q=quartile C=category *'=Cardiovascular mortality **'=Coronary disease death

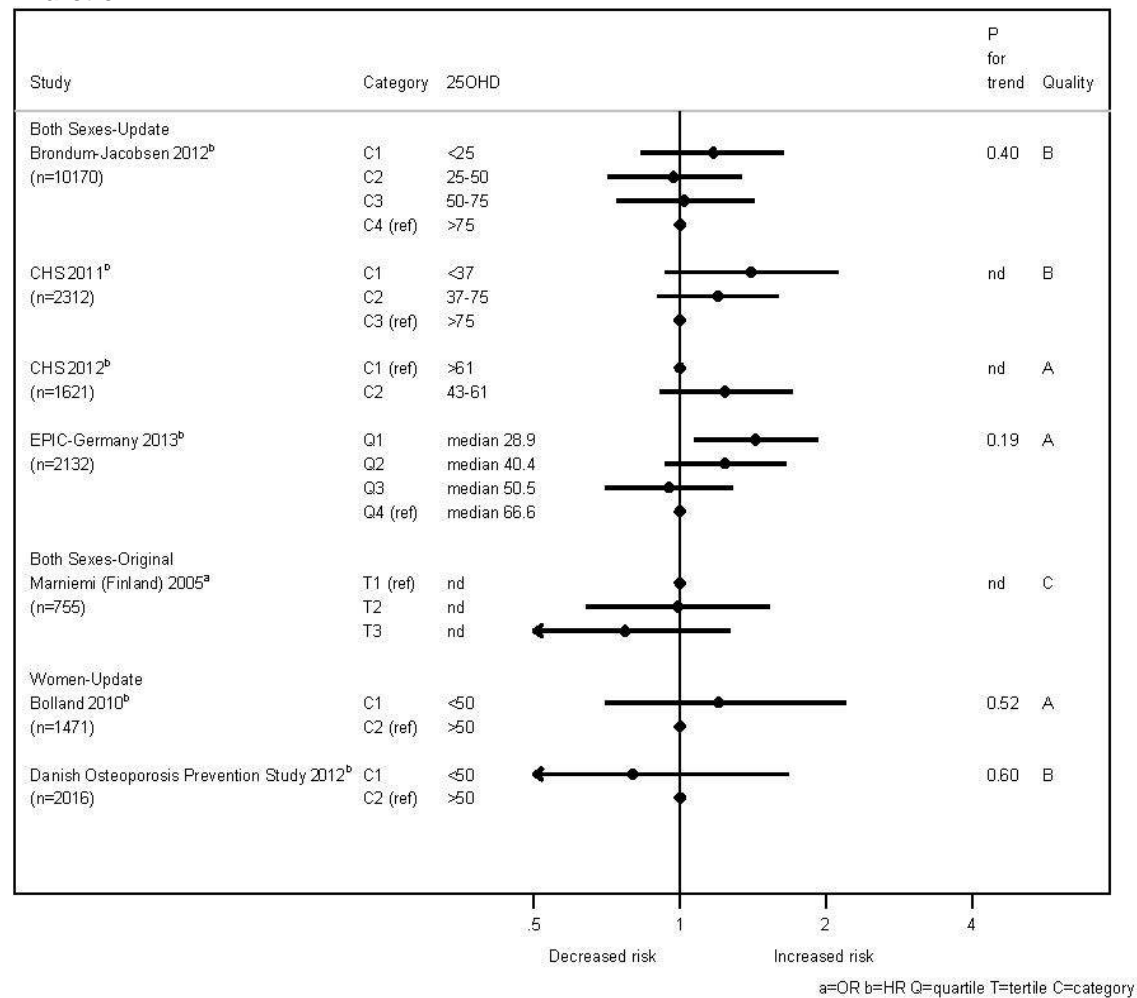
Abbreviations: InChianti = Invecchiare nel Chianti; CHS = Cardiovascular Health Study; NHANES = National Health and Nutrition Examination Study; ESTHER = EStrogen and THromboEmbolic Risk Study

Figure 6d. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality by gender



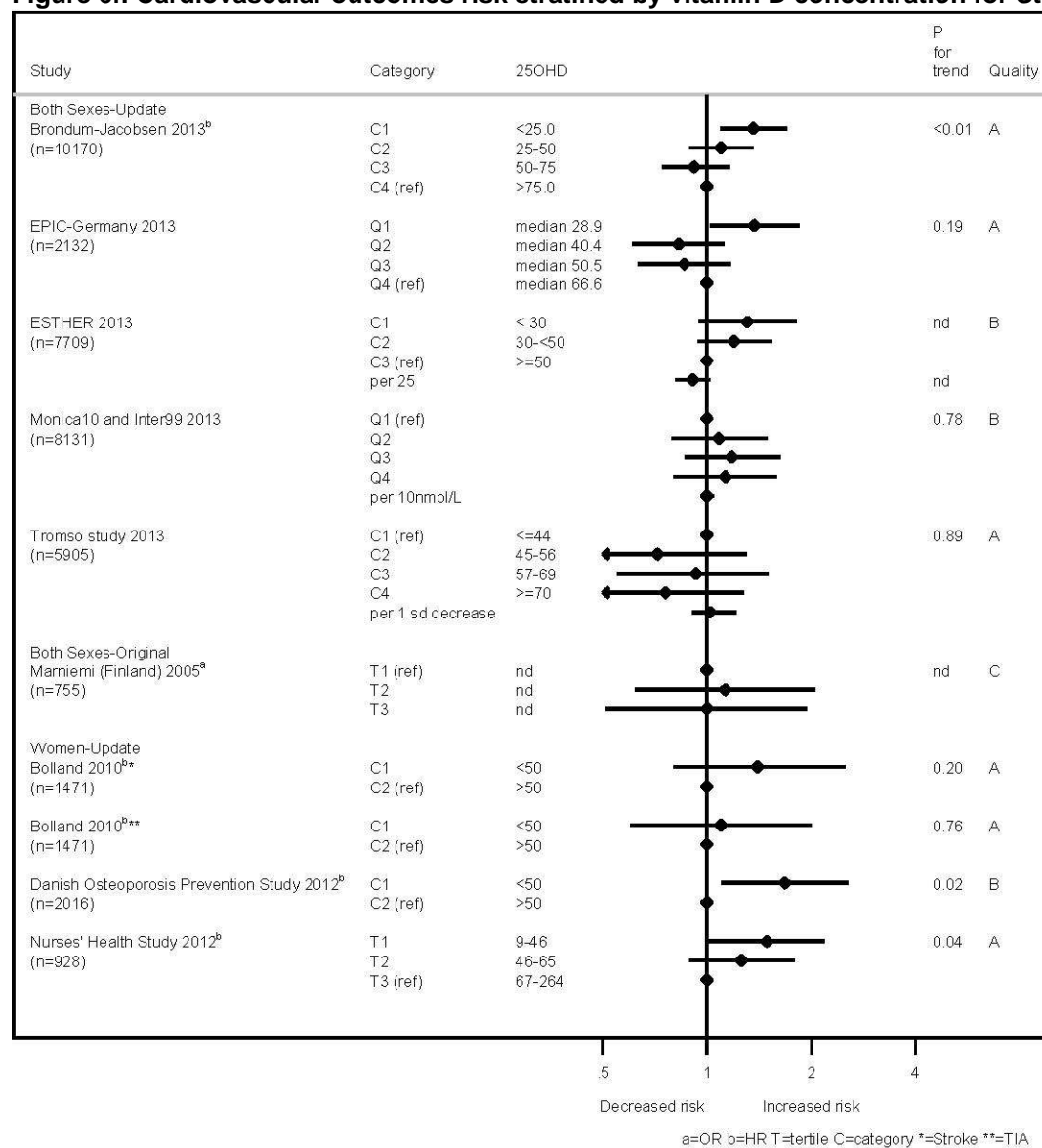
Abbreviation: WHI = Women's Health Initiative

Figure 6e. Cardiovascular outcomes risk stratified by vitamin D concentration for myocardial infarction



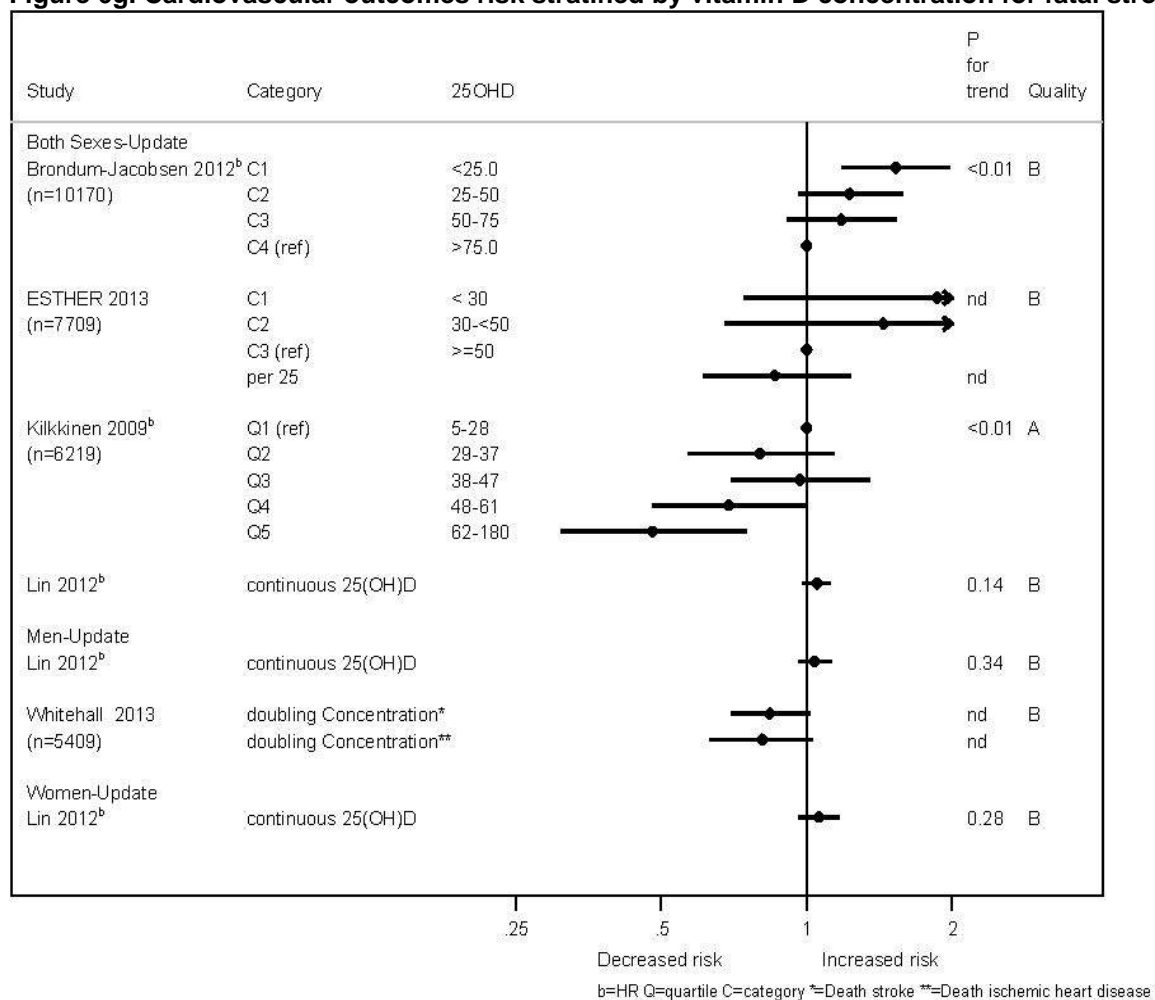
Abbreviations: CHS = Cardiovascular Health Study; EPIC = European Prospective Investigation into Cancer

Figure 6f. Cardiovascular outcomes risk stratified by vitamin D concentration for Stroke/TIA]



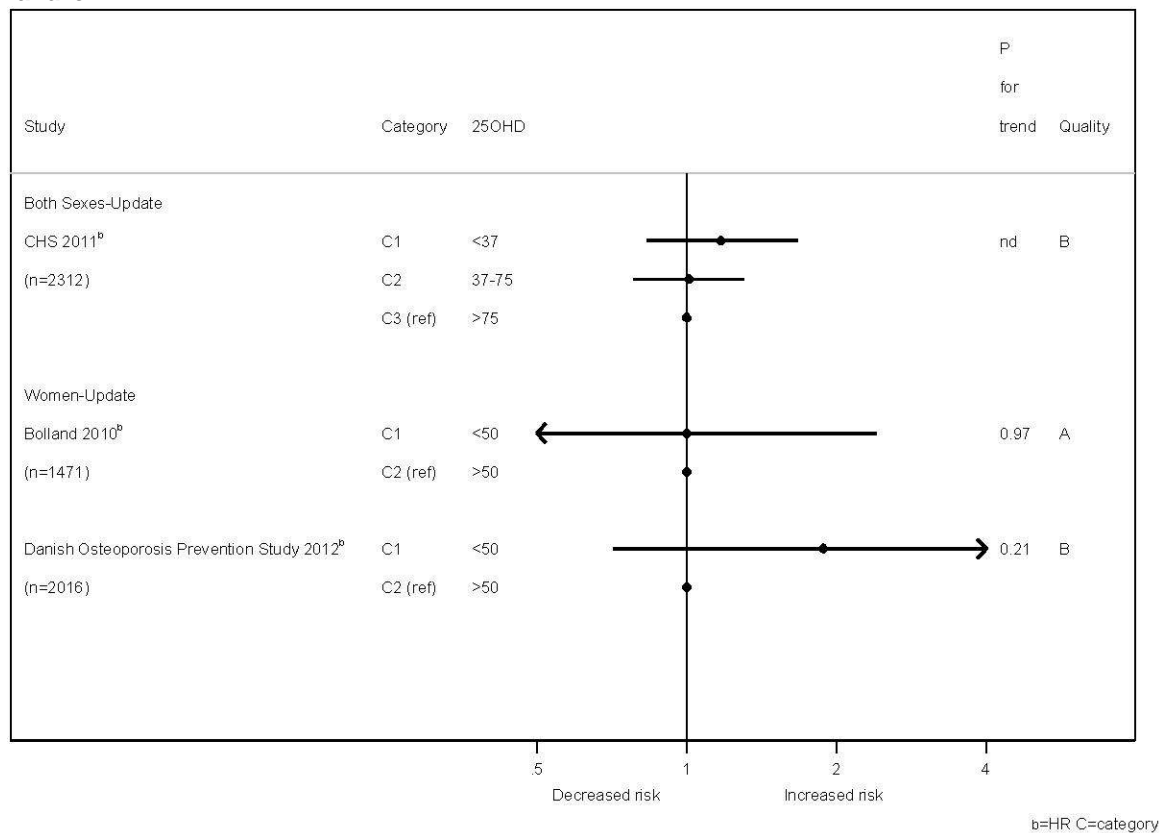
Abbreviations: EPIC = European Prospective Investigation into Cancer; ESTHER = EStrogen and THromboEmbolic Risk Study

Figure 6g. Cardiovascular outcomes risk stratified by vitamin D concentration for fatal stroke



Abbreviation: ESTHER = ESTrogen and THromboEmbolism Risk Study

Figure 6h. Cardiovascular outcomes risk stratified by vitamin D concentration for congestive heart failure



Abbreviation: CHS= Cardiovascular Health study

Vitamin D and Body Weight

The current report did not assess the association between serum 25(OH)D concentrations and body weight. The original report 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), only randomized controlled trials were included. 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 is considered to be the clinical outcomes). Only studies of adults were included. 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 and 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.⁹⁴ Two of the study arms included hormone replacement treatment and are not further discussed here. The remaining two arms compared vitamin D₃ 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.⁹⁵ The participants' mean baseline serum 25(OH)D concentration was 53 nmol/L. The trial compared vitamin D₂ 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.⁹⁶ The participants' mean baseline serum 25(OH)D concentration was about 33 nmol/L. The trial compared vitamin D₃ 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 [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments	
Heikkinen 1997 ⁹⁴ Kuopio ORFPS Kuopio, Finland (63°N) [9405029]	<ul style="list-style-type: none">• 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 ⁹⁵ Tromsø, Norway (70°N) [19056900]	<ul style="list-style-type: none">• 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 ⁹⁶ New Delhi, India (28.5°N) [19125756]	<ul style="list-style-type: none">• 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 [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	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 ⁹⁴ 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 ⁹⁵ [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 ⁹⁶ 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				

^AEstimated from reported data

^BPer estimated 95% confidence interval, P=0.17

Note: Outcomes cells are shaded for the Control rows.

Vitamin D and Cancer

This section explores 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. **No new RCTs were identified for the current report that addressed the effect of vitamin D or vitamin D combined with calcium on the risk for total cancer or cancer mortality. One cohort study found no association between total (all-cause) cancer and 25(OH)D concentrations (rated A), whereas a second cohort study observed an association in men but not in women (rated B). Ten cohort studies and one nested case control study addressed the association of serum 25(OH)D concentrations and cancer mortality. Five of the cohort studies (1 rated A, 4 rated B) observed no association of serum 25(OH)D concentration with total cancer mortality. Three cohort studies and the nested case control study observed a trend toward increased risk with decreased serum 25(OH)D (all rated B). One analysis using updated NHANES III data (rated B) observed a trend toward increasing risk for death with increasing serum 25(OH)D among men at higher latitudes whose blood was drawn in summer but the reverse in women. One cohort study observed a U-shaped association of increasing mortality with both low and high serum 25(OH)D.**

One RCT in the original report showed no effect of combined vitamin D₃ (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 D₃ (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 United States) showed no significant association between baseline 25(OH)D concentrations and total cancer mortality.

Detailed Presentation (Tables 14, 15, 16, & 17)

Two cohort studies were identified for the current report that assessed the association between serum 25(OH)D and all-cause cancer. The Cardiovascular Health Study, conducted in four U.S. cities, tracked white adults 65 and over for a median of 11 years and found no association of cancer with seasonally adjusted serum 25(OH)D concentrations (rated A).⁸⁷ The ESTHER Study, conducted in Germany, tracked 9,580 men and women ages 50 to 74 for more than 8 years: this study found an association between decreased serum 25(OH)D and increased risk for any cancer in men but not in women (rated B).⁹⁷

Eight observational studies were identified for the current report that assessed the association of serum 25(OH)D with cancer mortality.

The MrOS study, which followed men 65 and over in six U.S. cities for a 7.3-year followup, found an association of cancer mortality with serum 25(OH)D concentrations within the range clinically defined as vitamin D deficient but not with the lowest quartile of serum 25(OH)D (rated B).⁹⁸

The Whitehall Study, a British study of 5,409 men with a followup of 13 years, observed a trend toward increasing risk for total cancer mortality with decreasing serum 25(OH)D (rated B).⁷⁵

A substudy in 2,429 postmenopausal women within the Women's Health Initiative with measured baseline 25(OH)D concentrations were followed for 10 years. No association was seen between cancer mortality and serum 25(OH)D concentrations (rated A).⁷⁰

The ESTHER Study observed a significant association between serum 25(OH)D in the lowest quartile and increased risk for total cancer mortality (rated B).⁷⁶

The Copenhagen City Heart Study, which followed 9,791 adults for 28 years, observed no association between serum 25(OH)D and total cancer mortality (rated B).⁹⁹

The General Population Trial of Linxian followed 29,584 men and women (40–69 years of age), of whom 217 died of cancer. No association was seen between serum 25(OH)D and risk for cancer death (rated B).⁸³

The Southern Community Cohort Study, which followed some 85,000 men and women, ages 40 to 79 (about two-thirds of whom were African American), also observed no significant association between serum 25(OH)D concentrations and cancer death. No differences were seen between African Americans and whites or between men and women (rated A)⁷⁴

An assessment of NHANES III data that stratified men and women by latitude and season of blood draw and followed them for an average of 13.4 years found a trend toward increased risk for cancer death with increasing serum 25(OH)D among men in higher latitudes with summer blood sampling but a decreased risk among women in this category; cancer deaths were not independently verified in this study(B).¹⁰⁰

The Uppsala Longitudinal Study of Adult Men followed a population of elderly men (average age 71 years) for an average 12.7 years. This study observed a U-shaped association: both lower and higher serum 25(OH)D were associated with higher cancer mortality (<10th percentile: adjusted HR 1.99 [1.29, 3.08]; >90th percentile: adjusted HR 1.56 [0.95, 2.56]) (rated B).⁸⁴

The Tromsø Study followed 7,161 men (age 55 to 74) and women (age 50 to 74), of whom 498 died of cancer over 11.7 years. A non-significant trend was observed between decreasing serum 25(OH)D and increasing cancer mortality (rated B).⁷⁹

A nested case-control study conducted within the EPIC study that matched 541 individuals who died of colorectal cancer (CRC) with 661 controls (half were men; average age at diagnosis was 62) observed a small but significant trend toward increasing risk for CRC death and lower serum 25(OH)D however it was noted that a high proportion of the women in the cohort were taking bisphosphonates to prevent osteoporosis, which could have affected risk for cancer and mortality (rated B).¹⁰¹

From the original report, a 4-year population-based RCT,¹⁰² sampled from a 9 county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D₃ (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% 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 D₃ plus calcium group changed to 0.55 (95% CI 0.24, 1.28).

Another 5-year RCT compared the effects of supplemental vitamin D₃ (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).⁶⁶ 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 D₃ supplementation had no significant effect on the prevention of total cancer mortality (HR 0.86; 95% CI 0.61, 1.20) or incidence (HR 1.09; 95% 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^{85,103} or in subgroup analyses by either season or latitude after a median 9 years of follow up.¹⁰³

Findings by Age, Sex and/or Ethnicity

Of the studies identified for the current report, only one assessed differences in the association of serum 25(OH)D with total cancer mortality by ethnicity and saw no differences.⁷⁴ The analysis of NHANES III data observed apparently opposite associations between serum 25(OH)D concentrations between men and women of northern latitudes, as described above.¹⁰⁰

Among studies identified for the original report, 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 D₃ (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% CI 0.83 to 1.78; ≥100 nmol/L: RR = 1.35; 95% CI 0.78 to 2.31; P for trend=0.08]. However, this relationship was not seen in women (P for trend=0.12).¹⁰³ 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**
No studies identified for the current report assessed the association between serum 25(OH)D and total cancer mortality by age. Analyses using NHANES 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 D₃ (100,000 IU every 4 months) and placebo.
- **Postmenopause**
One assessment of postmenopausal women identified for the current study observed no association of serum 25(OH)D concentrations with total cancer death. One RCT with healthy postmenopausal women showed no effect of vitamin D₃ supplementation (1000 IU/d) on the risk of total cancer.
- **Pregnant & lactating women**
No Data

Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2007 ¹⁰² Nebraska, US (41° N) [17556697]	<ul style="list-style-type: none"> • 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 ⁶⁶ Oxford, UK (52°N) [12609940]	<ul style="list-style-type: none"> • 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%

^ANo difference between the vitamin D and the placebo arm.

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report)

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 ¹⁰³ NHANES III US (various) [16481636]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 44 (≥17) 45	<ul style="list-style-type: none">• 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 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
New Studies:												
Cawthon, 2010 ⁹⁸ MrOS	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	>80% excellent/good health status 74 (≥65) 100%			Cancer mortality stratified by baseline 25(OH)D quartiles and tertiles	X	X	X	X	X	X	MrOS study
de Boer, 2012 ⁸⁷ US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 74 (SD 4.6) 30%			Cancer stratified by baseline 25(OH)D median		X	X	X		X	
Eaton, 2011 ⁷⁰ US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 65.1 (7.6) 0%			Cancer mortality stratified by baseline 25(OH)D quartiles			X	X	X	X	

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report) (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	
Freedman, 2010 ¹⁰⁰ US (various)	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), 44.5 y • Male 87.8% (%) 		Total cancer mortality stratified by baseline 25(OH)D sextiles		X	X		X	X	
Hutchinson, 2010 ⁷⁹ Tromso Tromso, Norway	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y nd • Male nd (%) 		Cancer mortality stratified by baseline 25(OH)D quartiles		X	X	X		X	
Lin, 2012 ⁸³ Linxian, China	<ul style="list-style-type: none"> • Health status Healthy, Hypertension • Mean age (SD), 56.5 (SD 7.9) y • Male 55% (%) 		Cancer mortality stratified by baseline 25(OH)D tertiles		X	X	X		X	
Michaelsson, 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	<ul style="list-style-type: none"> • Health status More than 1/3 being treated for hypertension • Mean age (SD), 71 (SD 0.6) y • Male 100% (%) 		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X	X	X	X	
Signorello, 2013 ⁷⁴ Southern Community Cohort Study US	<ul style="list-style-type: none"> • Health status nd • Mean age (SD), y nd • Male nd (%) 					X			X	

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report) (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	
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 62 (SD 6.5) 43.8%	Cancer mortality stratified by baseline 25(OH)D tertiles	X	X		X	X	X	
Ordonez-Mena ⁹⁷ Saarland. Germany	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	nd NR (50–74) 54%	Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X			X	
Afzal 2013 ⁹⁹ Denmark	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 58 (47–65) NR	Cancer mortality stratified by baseline 25(OH)D category		X	X			X	
New nested case-control studies:										
Fedirko, 2012 ¹⁰¹ EPIC Multiple Countries	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 62.1 (SD 7.2) 40.5%			X	X	X	X	X	

Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report]

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 ¹⁰² Nebraska, US (41° 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 ⁶⁶ [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					

Note: Outcomes cells are shaded for the Control rows.

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report)

Author Year	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
[PMID]										
Freedman 2007 ¹⁰³	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		
NHANES III				62.5 to <80	117	3713	1.02	0.69, 1.50		
US				80 to <100	80	4218 (total, ≥80 nmol/L)	1	0.71, 1.40		
				100 to <120	41		0.92	0.58, 1.46		
[16481636]				≥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	1.4	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		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year		Outcome	Followup							
Study Name [PMID]	Life Stage	(n/N; Incidence)	Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
	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		
NEW Cohort Studies										
Cawthon 2010 ⁹⁸	Men 65 and over			Q 1: <49.8 nmol/L	NR	372	0.52	0.27, 1.00	0.086	
MrOS US (6 sites)				Q 2: 49.8≥ to <63 nmol/L	NR	370	0.90	0.51, 1.60		
				Q 3: ≥63to <75 nmol/L	NR	372	0.80	0.45, 1.41		
		cancer mortality	7.3 yrs	Q 4: ≥75 nmol/L	NR	376	1.00	reference		B
				Deficient, <50 nmol/L	NR	376	0.51	0.27, 0.98	0.044	
				Insufficient, 50 to <75 nmol/L	NR	737	0.85	0.52, 1.40		
				Sufficient, ≥75 nmol/L	NR	377	1.00	reference		
				per SD decrease	NR	1490	0.80	0.64, 0.99	NR	
de Boer 2012 ⁸⁷	Adults 65 and over	cancer	11 yrs	Normal level	259	1126	1.00	Reference	NR	A
Cardiovascular Health Study US (4 sites)				Low level (season specific, ranges 43–61 nmol/L)	111	495	1.13	0.90, 1.42		
Eaton 2011 ⁷⁰	Postmenopausal women	cancer mortality	10 yrs	Q 1: 3.25–36.50 nmol/L	nd	608	1.39	0.88, 2.19	0.11	
WHI US (multisite)				Q 2: 36.51–49.95 nmol/L	nd	606	1.22	0.79, 1.89		A
				Q 3: 49.96–65.38 nmol/L	nd	608	1.12	0.72, 1.72		
				Q 4: 65.39–146.67 nmol/L	nd	607	1.00	Reference		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year	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 2010 ¹⁰⁰										
NHANES III US (multisite)	men & women, all seasons	total cancer mortality	13.4 yrs	< 37.5 nmol/L	116	2689	RR = 1	Reference	0.43	B
				37.5–<50 nmol/L	174	3056	1.04	0.77, 1.41		
				50–<62.5 nmol/L	165	3143	1.23	0.89, 1.69		
				62.5–80 nmol/L	200	3713	1.19	0.86, 1.65		
				80–<100 nmol/L	139	2521	1.12	0.80, 1.57		
				≥100 nmol/L	90	1697	1.15	0.79, 1.68		
	men & women, winter/lower latitude	total cancer mortality	< 37.5 nmol/L	55	2689	1.00	Reference	0.23		
			37.5–<50 nmol/L	79	3056	1.3	0.77, 2.19			
			50–<62.5 nmol/L	57	3143	1.2	0.64, 2.26			
			62.5–80 nmol/L	78	3713	1.67	0.98, 2.86			
			80–<100 nmol/L	54	2521	1.31	0.77, 2.23			
			≥100 nmol/L	32	1697	1.5	0.74, 3.02			
	men & women, summer/ higher latitude	< 37.5 nmol/L	61	2689	1.00	Reference	0.67			
		37.5–<50 nmol/L	95	3056	0.91	0.63, 1.32				
		50–<62.5 nmol/L	108	3143	1.19	0.78, 1.82				
		62.5–80 nmol/L	122	3713	1.02	0.67, 1.54				
		80–<100 nmol/L	85	2521	1.03	0.66, 1.63				
		≥100 nmol/L	58	1697	1.02	0.63, 1.45				
	men, all seasons	< 37.5 nmol/L	47	2689	1.00	Reference	0.09			
		37.5–<50 nmol/L	95	3056	1.66	0.98, 2.80				
		50–<62.5 nmol/L	90	3143	1.43	0.90, 2.26				
		62.5–80 nmol/L	122	3713	1.52	0.82, 2.80				
		80–<100 nmol/L	90	2521	1.66	1.06, 2.61				
		≥100 nmol/L	69	1697	1.85	1.02, 3.35				
men, winter/lower latitude	< 37.5 nmol/L	25	2689	1.00	Reference	0.55				
	37.5–<50 nmol/L	51	3056	2.58	1.37, 4.87					
	50–<62.5 nmol/L	31	3143	1.14	0.48, 2.70					
	62.5–80 nmol/L	52	3713	1.99	0.86, 4.13					
	80–<100 nmol/L	33	2521	1.42	0.74, 2.72					
	≥100 nmol/L	23	1697	1.94	0.69, 5.45					

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year	Outcome	Followup Duration	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Study Name [PMID]	Life Stage	(n/N; Incidence)	(Time to Dx)						
	men, summer/higher latitude		< 37.5 nmol/L	22	2689	1.00	Reference	0.045	
			37.5–<50 nmol/L	44	3056	1.28	0.51, 3.23		
			50–<62.5 nmol/L	59	3143	1.55	0.81, 2.99		
			62.5–80 nmol/L	70	3713	1.33	0.53, 3.53		
			80–<100 nmol/L	57	2521	1.76	0.87, 3.57		
			≥100 nmol/L	46	1697	1.84	0.85, 3.98		
	women, all seasons		< 37.5 nmol/L	69	2689	1.00	Reference	0.29	
			37.5–<50 nmol/L	79	3056	0.85	0.59, 1.22		
			50–<62.5 nmol/L	75	3143	1.25	0.82, 1.90		
			62.5–80 nmol/L	78	3713	1.11	0.69, 1.79		
			80–<100 nmol/L	49	2521	0.86	0.50, 1.46		
			≥100 nmol/L	21	1697	0.64	0.35, 1.18		
	women, winter/lower latitude		< 37.5 nmol/L	30	2689	1.00	Reference	0.42	
			37.5–<50 nmol/L	28	3056	0.74	0.36, 1.51		
			50–<62.5 nmol/L	26	3143	1.27	0.51, 3.18		
			62.5–80 nmol/L	26	3713	1.44	0.61, 3.38		
			80–<100 nmol/L	21	2521	1.28	0.50, 3.24		
			≥100 nmol/L	9	1697	1.01	0.26, 3.90		
	women, summer/higher latitude		< 37.5 nmol/L	39	2689	1.00	Reference	0.03	
			37.5–<50 nmol/L	51	3056	0.88	0.54, 1.43		
			50–<62.5 nmol/L	49	3143	1.18	0.65, 2.12		
			62.5–80 nmol/L	52	3713	0.99	0.52, 1.87		
			80–<100 nmol/L	28	2521	0.7	0.34, 1.44		
			≥100 nmol/L	12	1697	0.52	0.25, 1.10		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year		Outcome	Followup Duration							
Study Name [PMID]	Life Stage	(n/N; Incidence)	(Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Hutchinson 2010 ⁷⁹ Tromsø Study Norway	Men (55–74 years) Women (50–74 years)	cancer mortality	11.7 yrs	Quartile 1: mean=33.8 (sd=7.6)	72	1184	1.14	0.80–1.63	NR	B
				Quartile 2: mean=46.7 (sd=6.0)	69	1187	1.13	0.80–1.61		
				Quartile 3: mean=56.2 (sd=6.0)	74	1192	1.23	0.87–1.75		
				Quartile 4: mean=72.3 (sd=13.2)	58	1188	1.00	Reference		
	non-smokers			Quartile 1: mean=33.8 (sd=7.6)	55	597	0.82	0.56–1.21	NR	
				Quartile 2: mean=46.7 (sd=6.0)	54	606	0.86	0.59–1.26		
				Quartile 3: mean=56.2 (sd=6.0)	60	607	1.02	0.70–1.48		
				Quartile 4: mean=72.3 (sd=13.2)	56	600	1.00	Reference		
		smokers								
Lin 2012 ⁸³ General Population Trial of Linxian China	Men (40–69 years)	cancer deaths	24 yrs	continuous 25(OH)D	217	1101	0.97	0.89, 1.05	0.406	B
				continuous 25(OH)D	141	608	1.00	0.91, 1.10	0.967	
	women			continuous 25(OH)D	76	493	0.88	0.75, 1.03	0.115	

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year	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
Michaelsson 2010 ⁸⁴	Elderly men (mean age 71)	cancer mortality	12.7 yrs	< 10th percentile (<46 nmol/L)	27	119	1.99	1.29, 3.08		B
Uppsala Longitudinal Study of Adult Men Sweden				10th–90th percentile (46–93 nmol/L)	118	956	1.00	Reference		
				>90th percentile (>93 nmol/L)	19	119	1.56	0.95, 2.56		
Signorello 2013 ⁷⁴	Men and women (40–79 years, 2/3 African American)	cancer death	NR	Quartile 4: (>54.1 nmol/L)	115	228	OR = 1	Reference	0.53	A
Southern Community Cohort Study				Quartile 3: 37.9–>54.1 nmol/L)	102	228	OR = 0.79	0.52, 1.21		
				Quartile 2: (25.45– 37.9 nmol/L)	127	255	OR = 1.03	0.66, 1.59		
				Quartile 1: <25.45 nmol/L)	133	243	OR = 1.28	0.78, 2.11		
Tomson 2013 ⁷⁵ Whitehall study		Death, cancer	13.1 yrs	Doubling Concentration	809	5409	0.84	0.71, 1.00		B
Schottker 2013 ⁷⁶ ESTHER		cancer mortality	9.5 yrs	<30	90	1439	1.42	1.08, 1.87		B
				30–50	172	4188	1.04	0.83, 1.29		
				>50	171	3927	1.00	Reference		
Afzal 2013 ⁹⁹		all cancer	28 yrs	50% reduction in plasma levels	2488	9791	1.06	1.02, 1.11		B
Ordonez-Mena ⁹⁷		total cancer	8 yrs	Q1	235	2253	1.10	0.93, 1.30		B
				Q2+Q3	396	4500	1.00	Reference		
				Q4	242	2254	1.12	0.95, 1.32		
NEW Nested case-control study										
Fedirko 2012 ¹⁰¹	Men and women (age at diagnosis approximately 62)	colorectal cancer specific mortality	73 mos	<36.3	104	242	1.00	Reference	0.04	B
EPIC				36.4–48.6	85	239	0.76	0.56, 1.02		
				48.7–60.5	95	241	0.93	0.69, 1.24		
Europe (multinational)				60.6–76.8	78	240	0.78	0.58, 1.06		
				>76.8	82	240	0.69	0.50, 0.93		

*Statistically significant (P<0.05)

Prostate Cancer

Synopsis

No qualified systematic reviews have evaluated the association between serum 25(OH)D concentrations and incidence of prostate cancer. **In the current report, one prospective cohort study and four nested case control studies (2 rated A, 3 rated B) found no association between baseline serum 25(OH)D concentrations and risk for prostate cancer. Two nested case-control studies (2B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer. In one study this increase was seen only among men whose sera were sampled in Summer or Autumn; in the other study, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency (concentrations less than 50nmol/L being considered deficient, 50–75nmol/L insufficient, and 75–125nmol/L considered sufficient). In the original report, eight nested case-control studies (2 rated B, 6 C) 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-rated study suggested a U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.**

Detailed Presentation (Tables 18 & 19; Figure 7)

For the current report, a total of one prospective cohort and six nested case-control studies reported on the association between baseline serum 25(OH)D concentrations and the risk for prostate cancer.¹⁰⁴⁻¹⁰⁹ The cohort study and four of the six nested case-control studies observed no association between serum 25(OH)D and risk for prostate cancer. No studies identified an association between lower serum 25(OH)D and increasing overall risk for prostate cancer. One study, a nested case-control within the Health Professionals' Followup Study, found an association between lower baseline serum 25(OH)D and increasing risk for lethal prostate cancer (adjusted OR 0.44 [0.24, 0.79] (comparing the lowest with the highest quartile of 25(OH)D), with no effect of time to diagnosis (rated A).¹⁰⁸ Three nested case-control studies (two rated A and one B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer.¹⁰⁵⁻¹⁰⁷ In one study this increase was seen only among men whose sera were sampled in Summer or Autumn;¹⁰⁶ in another study, the Multiethnic Cohort, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency.¹⁰⁷ The number of cases in the nested case control studies ranged from 297 to 2,106. The methodological quality of two studies was B, and four were rated A.

In the original report, 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.^{103,110-122} The number of cases ranged from 61 to 749. The latitudes of the studies ranged

from 21° N to 60° 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.

Ten studies **identified for the original report** 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.^{110,112-119,122} One study found no association between baseline serum 25(OH)D concentrations and mortality from prostate cancer.¹¹⁴ 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).¹¹¹ 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% 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% 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% CI 0.8, 2.7) compared to the group with a 25(OH)D concentration of 40 to 49 nmol/L.¹²⁰ 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)₂D

Five studies reported on the association between 1,25(OH)₂D serum concentrations and the risk of prostate cancer. Four studies did not find an association.^{115,118,119,122} One study found that the risk of prostate cancer decreased with higher serum concentrations of 1,25(OH)₂D in men with low serum concentrations of 25(OH)D (unadjusted OR 0.15, comparing 4th quartile of 1,25(OH)₂D (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).¹¹⁴ 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**

None of the studies in the update report focused on younger participants. Two

studies **in the original report** provided data on younger subjects. Ahonen et al. analyzed subjects from 40 to 57 years of age.¹¹¹ 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.¹⁰³ **In the original report**, 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% 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% 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**

All of the studies identified for the update report included men whose average age was 60 or higher. One cohort included only men 65 and older¹⁰⁴ Only one study reported on effect of age at diagnosis. No studies identified an association between lower serum 25(OH)D and increasing overall risk for prostate cancer. One study, a nested case-control within the Health Professionals' Followup Study, found an association between lower baseline serum 25(OH)D and increasing risk for lethal prostate cancer (adjusted OR 0.44 [0.24, 0.79] (comparing the highest to the lowest quartile of 25(OH)D), with no effect of time to diagnosis.¹⁰⁸ Three nested case-control studies (2B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer.¹⁰⁵⁻¹⁰⁷ In one study this increase was seen only among men whose sera were sampled in Summer or Autumn;¹⁰⁶ in another study, the Multiethnic Cohort, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency.¹⁰⁷ In the original report, 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% 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% 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% 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 observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Ahn 2008 ¹¹⁰ PLCO US (21°N to 44°N) [18505967]	Health status	8% current smoker	Assay	RIA (Heartland)	Prostate cancer risk stratified by baseline 25(OH)D quintiles	X		X	X		X	
	Mean age (range/SD), y	67.8 (5.3)										
	Male (%)	100	Season nd blood drawn									
Platz 2004 ¹¹⁹ Mikhail 2007 ¹¹⁷ HPFS US (multiple latitudes) [15090720] [17440943]	Health status	Smoked 18%; DM 3.6%	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	6% nonwhite
	Mean age (range/SD), y	66 (7)										
	Male (%)	100	Season nd blood drawn									
Freedman 2007 ¹⁰³ NHANES III US (multiple latitudes) [17971526]	Health status	28% current smoker	Assay	RIA	Prostate cancer mortality stratified by 2 baseline 25(OH)D categories	X	X	X	X	X	X	71% white; 14% black; 6% Hispanics
	Mean age (range/SD), y	44										
	Male (%)	100	Season blood drawn	South: Nov to Mar; North: Apr to Oct								
Tuohimaa 2004 ¹²⁰ Helsinki Heart Vasterbotten; Janus Project; Finland (60°N) [14618623]	Health status	Gemfibrozil vs. placebo subjects	Assay	RIA (Incstar)	Prostate cancer risk stratified by 5 baseline 25(OH)D categories		X			X		
	Mean age (range/SD), y	<40 to >60										
	Male (%)	100	Season nd blood drawn									

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Li 2007 ¹¹⁶ Gann 1996 ¹²² PHS US (multiple latitudes) [17388667] [8850273]	Health status	on ASA, β - carotene, placebo trial; 9% current smoker 58.9 (8.3)	Assay	RIA (Bruce Hollis)	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X				X	94% white
Corder 1993 ¹¹⁴ San Francisco US (37°N) [8220092]	Health status Mean age (range/SD), y Male (%)	nd 57 (38–81) 100	Assay	Competitive protein- binding (Haddad, 1971) nd	Prostate cancer risk compared by baseline 25(OH)D		X			X		50% black; 50% white
Ahonen 2000 ¹¹¹ Helsinki Heart Finland (60°N) [11075874]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 40–57 100	Assay	RIA (Incstar)	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X	X	X	X	
Nomura 1998 ¹¹⁸ Honolulu Heart US (21°N) [9794175]	Health status Mean age (range/SD), y Male (%)	64% smoked 58 (49–70) 100	Assay	Protein- binding nd	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	100% Japanese Americans
Tuohimaa 2007 ¹²¹ Helsinki Heart Finland (60°N) 17301263	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 51 (3.7) 100	Assay	RIA (Incstar)	Prostate cancer risk stratified by 3 baseline 25(OH)D categories		X	X	X			

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Jacobs 2004 ¹¹⁵ NPC Eastern US (25°46'N to 41°N) [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 ¹¹³ 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 ¹¹² 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
Braun 1995 ¹¹³ 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 ¹¹² 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

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
New nested case-control studies											
Barnett, 2010 ¹⁰⁴ MrOS US (various)	Health status Mean age (range/SD), y Male (%)	nd 73.6 (5.9) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	probably need to check another article from this study to get funding info	
Brandstedt, 2012 ¹⁰⁵ Malmo, Sweden	Health status Mean age (range), y Male (%)	nd 61.7 (NR, SD 6.4) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X			X	Malmo Diet and Cancer Study (MDCS)	
Meyer, 2013 ¹⁰⁶ Norway	Health status Mean age (range), y Male (%)	nd 48.2 (SD 9.2) 100%	Prostate cancer risk stratified by baseline 25(OH)D sextiles		X			X			
Park, 2010 ¹⁰⁷ Multiethnic Cohort Study	Health status Mean age (SD), y Male (%)	nd 68.7 (SD 7.2) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X		X					
Shui, 2012 ¹⁰⁸ Health Professionals' Followup Study US	Health status Mean age (SD), y Male (%)	nd 64.4 (SD 7.8) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X		
Travis 2009 ¹⁰⁹ European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	Health status Mean age (SD), y Male (%)	nd 60.5 (SD 6.2) 100%	Prostate cancer risk stratified by baseline 25(OH)D		X	X			X		

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	25(OH)D	Comparisons	Confounders/Effect Modifiers Adjusted					Lifestyles	Comments
				Nutrients	Demographic	Anthrop	Medical	UV Exposure		
NEW Cohort study										
Ordonez-Mena 2013 ⁹⁷	Health status	NR	Cancer mortality stratified by baseline 25(OH)D tertiles	X		X	X			confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer
ESTHER	Mean age	50–74								
Saarland, Germany	Male (%)	54%								

^AFor prevention of recurrence of non-melanoma skin cancer.

^BThis is a cohort study, not a nested case-control study.

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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 ¹¹⁰	51–70	Prostate cancer (741; 781)	2–8	12.8–42.5	119	157	1	Reference	0.2	B		
PLCO [8505967]				42.5–51.	125	156	1.1	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 ¹¹⁹	51–70	Prostate cancer (460; 460)	2.2 (mean)	Quartile 1 ^A	109	114	1	Reference	0.59	B		
Mikhak 2007 ¹¹⁷				Quartile 2	115	113	1	0.67, 1.49				
HPFS [15090720]				Quartile 3	94	120	0.77	0.51, 1.15				
[17440943]				Quartile 4	142	113	1.19	0.79, 1.79				
Freedman 2007 ¹⁰³	19–50	Mortality prostate cancer	nd	<62.5	22	nd	1	Reference	0.95	B		
NHANES III [17971526]				≥62.5	25	nd	0.91	0.39, 2.14				
Tuohimaa 2004 ¹²⁰	19–50	Prostate cancer (622; 1451)	≤9–>14 (range)	≤19	19	nd	1.5	0.8, 2.7		C		
Helsinki Heart [14618623]	51–70			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 ¹¹⁶	19–50	Prostate cancer (492; 664)	11 (median)	Quartile 1 ^B	nd	nd	1.01	0.71, 1.44	0.91	C		
PHS	51–70			Quartile 2	nd	nd	1.26	0.89, 1.80				
[17388667]				Quartile 3	nd	nd	1	0.71, 1.41				
				Quartile 4	nd	nd	1	Reference				

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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		
Gann 1996 ¹²² PHS [8850273]	19–50 51–70	Prostate cancer (232; 414)	6 (mean)	15.7–53.3	nd	nd	1	nd	0.82	C		
				53.4–70.9	nd	nd	1.1	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	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	nd	nd				
			53.4–70.9	nd	nd	1	nd					
			71–93.5	nd	nd	0.82	nd					
			93.6–194	nd	nd	0.76	0.39, 1.47					
Corder 1993 ¹¹⁴ [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 ¹¹¹ 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 ¹¹⁸ 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				

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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
Tuohimaa 2007 ¹²¹ Helsinki Heart	19–50 51–70	Prostate cancer (132; 456)	10.8 (mean)	<40 40–59 ≥60	- - -	- - -	1.88 1 1.25	1.15, 3.08* Reference 0.64, 2.43		C
[17301263]										
Jacobs 2004 ¹¹⁵ NPC	51–70	Prostate cancer (83; 166)	5.1 (mean)	20–63.3 63.4–81.9 82–149	26 33 24	58 49 59	1 1.71 0.75	Reference 0.68, 4.34 0.29, 1.91	0.51	C
[15225833]										
Braun 1995 ¹¹³ WCC [7612803]	19–50 51–70	Prostate cancer (61; 122)	14 (mean)	<60.1 60.1–73.8 73.9–88.5 88.6–103 >103	7 17 16 4 17	24 25 24 25 24	1 2.3 2.3 0.6 2.4 ^E	Reference 0.7, 7.8 0.7, 7.7 0.1, 2.5 0.8, 8.2	0.6	C
Baron 2005 ¹¹² CPP [15767334] ^F	19–50 51–70	Prostate cancer (70 cases in a total of 672) ^F	<4 (34%)	<62.9 62.9–84.9 85	nd nd nd	NA NA NA	1 1.22 0.32	Reference 0.66, 2.26 0.72, 2.43	0.7	C
NEW nested case-control studies										
Barnett 2010 ¹⁰⁴ MrOS	men 65 and over	Prostate Cancer (297 cases in a total of 1648)	NR	Quartile 1(7.75–49.75 nmol/L) Quartile 2(50.0–62.3 nmol/L) Quartile 3(62.5–74.8 nmol/L) Quartile 4 (75–189.0 nmol/L)	68 91 53 85	411 415 406 416	HR=1.00 1.35 0.64 1.20	Reference 0.91, 2.01 0.41, 1.00 0.81, 1.78	0.130 0.050 0.370	B
Brandstedt 2012 ¹⁰⁵	51–70 yrs; ≥71 yrs	Prostate Cancer (918; 924)	NR	Quartile 1(≤68nmol/L) Quartile 2(69–84nmol/L) Quartile3(85–102nmol/L) Quartile 4(≥103nmol/L)	206 237 245 230	242 232 226 224	1.00 1.25 1.37 1.34	Reference 0.95, 1.65 1.03, 1.82 0.99, 1.82	0.048	A

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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	
Meyer 2013 ¹⁰⁶		Prostate Cancer (2106;2106)	NR	<30nmol/L	72	92	IRR=0.82	0.58, 1.15		B	
				30–49nmol/L	528	553	1.02	0.87, 1.21			
				50–69nmol/L	718	771	1.00	Reference			
				70–89nmol/L	537	466	1.24	1.05, 1.47			
				≥90nmol/L	251	224	1.17	0.93, 1.48			
		30–nmol/L increase		NR	NR	1.13	1.02, 1.25				
		<30nmol/L		49	63	0.80	0.52, 1.23				
		30–49nmol/L		304	286	1.09	0.86, 1.40				
		50–69nmol/L		288	297	1.00	Reference				
		70–89nmol/L		145	128	1.14	0.85, 1.53				
		≥90nmol/L		38	50	0.74	0.46, 1.18				
		30–nmol/L increase		NR	NR	0.97	0.83, 1.14				
		<30nmol/L		13	14	0.97	0.45, 2.10				
		30–49nmol/L		132	172	0.87	0.66, 1.16				
		50–69nmol/L		296	329	1.00	Reference				
		70–89nmol/L		297	259	1.34	1.05, 1.71				
		≥90nmol/L		180	144	1.46	1.07, 2.00				
		30-nmol/L increase		NR	NR	1.25	1.08, 1.45				
Park 2010 ¹⁰⁷ multiethnic cohort	Men 45–75 yrs	Prostate Cancer (329, 656)	NR	Quartile 1: <57.3 nmol/L	82	163	1.00	Reference		A	
				Quartile 2: 57.3 <77.5 nmol/L	84	166	1.05	0.70, 1.58			
				Quartile 3: 77.5<99.8 nmol/L	72	172	0.81	0.52, 1.28			
				Quartile 4: ≥99.8 nmol/L	91	155	1.17	0.72, 1.89	0.600		
				Deficient: <50nmol/LL	53	106	1.10	0.68, 1.78			
				Insufficient: 50–75 nmol/L	98	204	1.04	0.73, 1.48			
				75–125 nmol/L	137	287	1.00	Reference			
				≥125 nmol/L	41	59	1.52	0.92, 2.51	0.320		

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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
Shui 2012 ¹⁰⁸				Quartile 1	41	325	1.00	Reference		A
Health Professionals' Followup Study	Lethal Prostate Cancer (209;1324)	5.2 years		Quartile 2	33	336	0.78	0.47, 1.30	0.002	
				Quartile 3	21	334	0.50	0.28, 0.88		
				Quartile 4	19	329	0.44	0.24, 0.79		
	Overall Prostate Cancer (1260;1324)	5.2 years		Quartile 1	310	325	1.00	Reference	0.45	A
				Quartile 2	298	336	0.93	0.74, 1.17		
				Quartile 3	319	334	0.99	0.79, 1.24		
				Quartile 4	333	329	1.07	0.86, 1.34		
	Advance stage at Diagnosis (166;1324)	5.2 years		Quartile 1	51	325	1.00	Reference	0.22	
				Quartile 2	43	336	0.96	0.61, 1.52		
				Quartile 3	32	334	0.63	0.39, 1.03		
				Quartile 4	40	329	0.85	0.53, 1.35		
	High Grade Prostate Cancer (239;1324)	5.2 years		Quartile 1	69	325	1.00	Reference	0.87	
				Quartile 2	55	336	0.81	0.54, 1.21		
				Quartile 3	51	334	0.75	0.50, 1.13		
				Quartile 4	64	329	0.99	0.67, 1.46		
Travis 2009 ¹⁰⁹				Quintile 1 (2.5–40.4nmol/L)	125	151	1.00	Reference		
European Prospective Investigation into Cancer and Nutrition (EPIC)	Prostate Cancer	4.1 years		Quintile 2(40.5–50.4 nmol/L)	143	150	1.27	0.89, 1.81	0.188	A
				Quintile 3(50.5– 59.1nmol/L)	128	151	1.23	0.85, 1.76		
				Quintile 4 (59.2– 70.8nmol/L)	114	150	1.06	0.73, 1.55		
				Quintile 5(70.9– 163.7nmol/L)	142	150	1.28	0.88, 1.88		
				Doubling Concentration	652	752	1.17	0.93, 1.47		

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	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
Ordonez-Mena 2013 ⁹⁷ ESTHER		Prostate Cancer	8 yrs	Q1	38	882	HR 1.16	0.78, 1.74		B
				Q2+Q3	66	1737	HR 1.00	Reference		
				Q4	67	1505	HR 1.21	0.86, 1.70		

*Statistically significant (P<0.05)

^ACut points separated by analytical run; season, distributions among control (see Table 3 in original study).

^BCut points based on control standardized by season of collection.

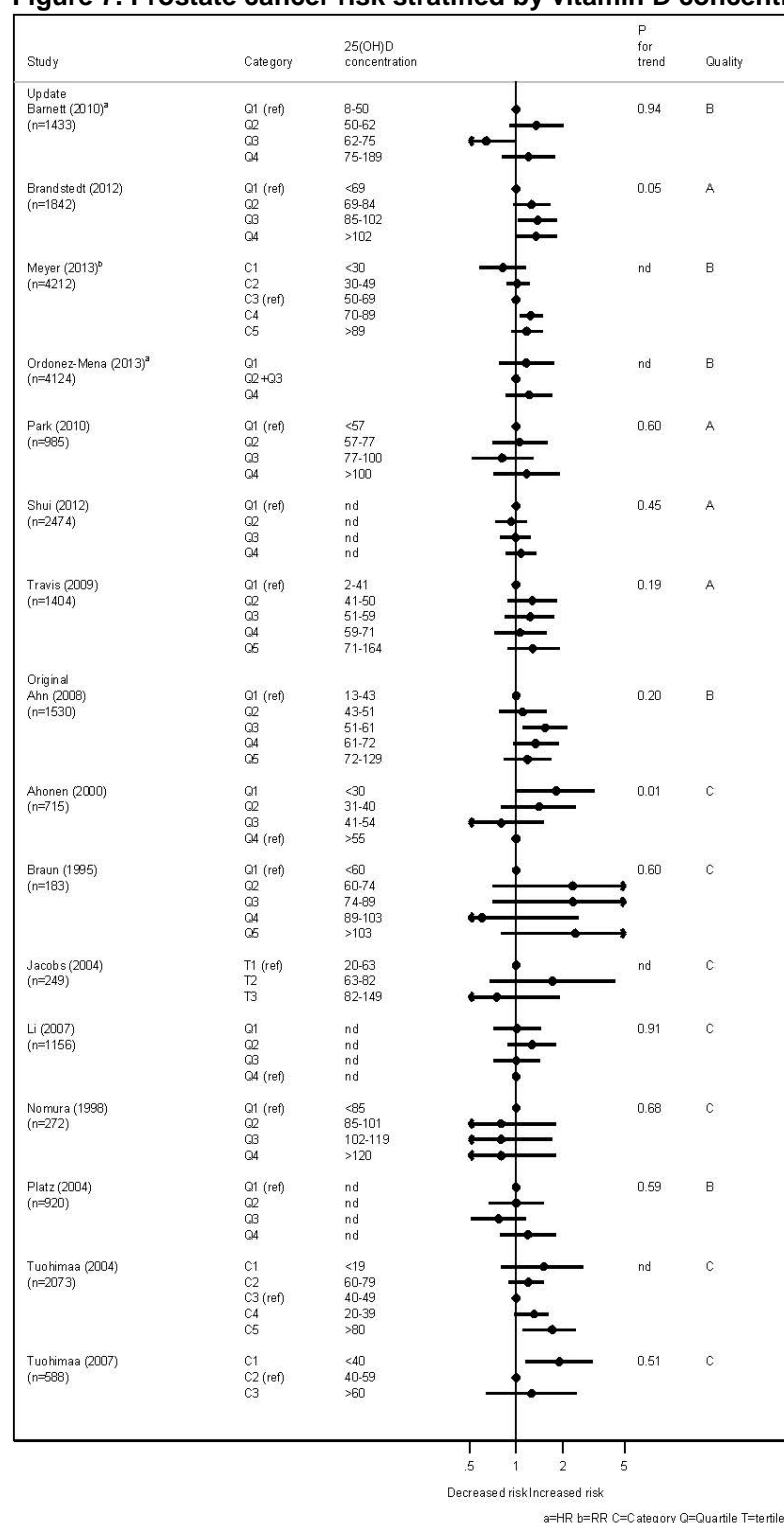
^CCut points based on total original cohort.

^DCut points based on control frequency.

^EUnadjusted.

^FThis is a cohort study, not a nested case-control study.

Figure 7. Prostate cancer risk stratified by vitamin D concentration (updated from original report)



Colorectal Cancer

Synopsis

No qualified systematic reviews have evaluated the association between 25(OH)D concentrations and colorectal cancer mortality or incidence. **No new RCTs and cohort studies that addressed the effect of vitamin D or vitamin D and calcium on colorectal cancer mortality or incidence were identified for the current report. Three nested case-control studies (2A, 1B) found trends of increasing colorectal cancer incidence with decreasing 25(OH)D concentrations. One nested case-control study (rated B) found no association between colorectal cancer and 25(OH)D. Two of these nested case-control studies (2B) also examined colon and rectal cancer as separate outcomes. One study reported a significant negative trend between 25(OH)D and colon cancer risk and the other found a non-significant negative trend. For rectal cancer, the same two studies reported either a negative trend or a small but non-significant negative trend with 25(OH)D.**

In the original report, one B quality RCT of elderly population reported no significant difference in colorectal cancer mortality or incidence between supplemental vitamin D₃ 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 Cancer (Tables 20 & 21)

In the original report, an RCT compared supplemental vitamin D₃ (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).⁶⁶ 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 D₃ 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 [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 2003 ⁶⁶ Oxford, UK (52°N) [12609940]	<ul style="list-style-type: none"> • 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%

Abbreviations: CVD = cardiovascular disease; HRT = hormone replacement therapy.

^ANo difference between the vitamin D and the placebo arm.

Table 21. Vitamin D and colorectal cancer: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 2003 ⁶⁶ [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					

Note: Outcomes cells are shaded for the Control rows.

Detailed Presentation of 25(OH)D Concentrations and Colorectal Cancer (Tables 22 & 23; Figures 8, 9, & 10)

Four nested case-control studies that assessed the association of serum 25(OH)D with colorectal cancer were identified for the current report. A nested case-control study conducted within the EPIC study that matched 1220 cases of colorectal cancer with 1222 controls found increasing risk for colorectal cancer with lower serum 25(OH)D.¹²³ This study was rated B for quality because cases were ascertained from cancer registries and were not verified independently. Two additional nested case-control studies, one nested in the Women's Health Initiative (WHI) and the other in the Multiethnic Cohort (both rated A), found increasing risk for colorectal cancer with lower 25(OH)D (the WHI is described further later in the section on vitamin D plus calcium).^{124,125} Another case-control study, nested in the Physicians' Health Study, found no association between colorectal cancer incidence and levels of 25(OH)D and 1,25(OH)2D in U.S. male physicians aged 40–84 years (rated B).¹²⁶

The studies nested in the EPIC and Physicians' Health cohorts also assessed colon and rectal cancer as separate outcomes. The nested case-control study within EPIC found a trend toward increasing risk for colon cancer incidence with lower 25(OH)D;¹²³ the study within the Physicians' Health cohort found a similar but non-significant trend.¹²⁶ For rectal cancer incidence, the Physicians' Health nested case-control study found a negative trend between 25(OH)D and rectal cancer, while the EPIC nested case-control found a small but non-significant negative trend.

From the original report, a total of seven nested case-control studies evaluated the associations between 25(OH)D concentrations and risk of colorectal cancer¹²⁷⁻¹³¹ or colon cancer.^{132,133} 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 III¹⁰³ 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 follow up 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 studies¹²⁷⁻¹³¹ were rated B and two were rated C.^{132,133} 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 study¹⁰³ 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 III¹⁰³ 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.^{132,133} 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).¹³³ Both studies reported no significant association between 25(OH)D concentrations and colon cancer risk by trend analysis.

In the original report, three studies, from the Japan PHC, HPFS, and ATBC respectively, provided data on adult men.¹²⁷⁻¹²⁹ 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).¹²⁹ The HPFS also reported a subgroup analysis on men aged 65 years or older.¹²⁹ 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.^{128,129} 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).¹²⁸

Two nested case-control studies from the NHS and Japan PHC provided data on adult women.^{128,130} 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).¹³⁰ 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).¹³⁰ The WHI focused on postmenopausal women.¹³¹ 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.¹²⁸

Findings per Special Populations

No subgroup data were available regarding the association between 25(OH)D concentrations and colorectal cancer risk in obese persons. **In the original report**, one study exclusively included male smokers aged between 50 and 69 years,¹²⁷ 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.¹³² 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.¹³⁰

Findings Excluding Early Cases

In the original report, 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.^{127,129,130} 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.¹²⁷ Otherwise, the results were not materially different from the main analysis.

Findings on 1,25-Dihydroxyvitamin D

The nested case-control study within the Physicians' Health cohort found no significant associations between 1,25(OH)₂D and colorectal, colon, and rectal cancer risk.¹²⁶

In the original report, a total of three studies evaluated the associations between 1,25(OH)₂D concentrations and colorectal cancer risk^{127,130} or colon cancer.¹³³ 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.¹²⁷

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**
Three of the nested case-control studies identified for the update report included people with mean age ranged from 59 to 69 years; a fourth study included individuals aged 40–84 (mean age was not reported). A trend between higher 25(OH)D levels and lower risk of colorectal cancer was found in three studies and one study found no association. Of the two studies that also assessed colon and rectal cancer outcomes separately, one study found significant negative trends between 25(OH)D and colon or rectal cancer and one study reported no association.
- **≥71 y**
In the original report, 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**
In the original report, 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 (updated from original report)

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 ¹⁰³ NHANES III US (various) [16481636]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 44 (≥17) 45	<ul style="list-style-type: none">• 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 ¹³³ WCC Maryland, US (38°N) [329893]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 55 (nd) nd	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Horris 1993) Fall	<ul style="list-style-type: none">• 25(OH)D levels between cases and controls• Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		
Feskanich 2004 ¹³⁰ NHS US (various) [15342452]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 60 (43–70) 0	<ul style="list-style-type: none">• 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 ¹³² WCC Maryland, US (38°N) [2572900]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 63 (nd) 50	<ul style="list-style-type: none">• Assay method• Season blood drawn	HPLA (Clemens 1982) Fall	<ul style="list-style-type: none">• 25(OH)D levels between cases and controls• Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		White: 100%

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies^A (updated from original report) (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		
Cohort												
Otani 2007 ¹²⁸ Japan PHC Japan (various) [17622244]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any Men: 57 (40–69); Women: 56 (40–69)	<ul style="list-style-type: none">• Assay method• Season blood drawn	CPBA (Haddad 1971) All	<ul style="list-style-type: none">• 25(OH)D levels between cases and controls• Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Tangrea 1997 ¹²⁷ ATBC Finland (~60°N) [9242478]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Smoker ^B 60 (50–69) 100	<ul style="list-style-type: none">• 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 ¹³¹ WHI US (various) [16481636]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Post-menopausal women ^C nd (50–79) 0	<ul style="list-style-type: none">• 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 ¹²⁹ HPFS US (various) [17623801]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Smoker 5% 66 (nd) 100	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Horris 1997) All	<ul style="list-style-type: none">• 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%

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies^A (updated from original report) (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
NEW Nested case-control studies											
Jenab 2010 ¹²³ European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	<ul style="list-style-type: none">Health statusMean age 58.6 (SD 7.2)Male (%) 49.7%	nd	<ul style="list-style-type: none">Colorectal cancer risk stratified by baseline 25(OH)D quintilesRectum cancer stratified by baseline 25(OH)D quintiles	X	X	X			X	X	age, % female is of controls-colon cancer
Lee, 2011 ¹²⁶ Physicians US (various cities)	<ul style="list-style-type: none">Health statusMean age nd (SD), yMale (%) 100	Healthy	<ul style="list-style-type: none">Colorectal cancer risk stratified by baseline 25(OH)D quartilesColon cancer stratified by baseline 25(OH)D quartiles	X	X	X			X	X	
Neuhouser, 2012 ¹²⁴ WHI US (various cities)	<ul style="list-style-type: none">Health statusMean age 65.1 (SD 6.8)Male (%) 0%	Post-menopausal	Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X				X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset
Woolcott, 2010 ¹²⁵ Multiethnic Cohort Study US, Hawaii/Los Angeles	<ul style="list-style-type: none">Health statusMean age 69.2 (SD 7.9)Male (%) nd	nd	Colorectal cancer risk stratified by baseline 25(OH)D sextiles		X	X					

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies^A (updated from original report) (continued)

Original Report) (Continued)				Confounders/Effect Modifiers Adjusted							Comments
Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV	Exposure	Lifestyle	
NEW Cohort study											
Ordonez-Mena 2013 ⁹⁷ ESTHER Saarland, Germany	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Nd NR (50–74) 54%	Colorectal cancer stratified by baseline 25(OH)D tertiles	X	X	X				X	confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

^AThis table is ordered alphabetically by study author.

^BParticipants of a lung cancer prevention 2 by 2 RCT of alpha-tocopherol and beta-carotene.

^CParticipants of a hip fracture prevention RCT of vitamin D3 and calcium.

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report)

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 ¹⁰³	19–50 ^A	Colorectal Cancer Mortality (66/16818; 0.004)	nd	<50	28	~5606	1	Reference	0.02	B
	51–70			50–80	24	~5606	0.44	0.20, 0.95*		
[17971526]	≥71			≥80	14	~5606	0.28	0.11, 0.68*		
Nested case-control study										
Colorectal cancer										
Men										
Otani 2007 ¹²⁸	19–50	Colorectal cancer (N=196 cases; 392 controls)	1–13	<57.2	43	74	1	Reference	0.39	B
Japan PHC	51–70 ^A			57.2–69.0	40	85	0.76	0.42, 1.4		
				69.0–80.2	36	85	0.76	0.39, 1.5		
[17622244]				≥80.2	44	80	0.73	0.35, 1.5		
Wu 2007 ¹²⁹	19–50	Colorectal cancer (179 cases; 356 controls)	1–9	46, median	45	71	1	Reference	0.24 ^B	B
HPFS	51–70 ^A			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	Colorectal cancer, age <65		48.2, median	25	34	1	Reference	0.13	
	51–70 ^A			66.8	15	28	1.03	0.36, 2.91		
				80	9	30	0.38	0.12, 1.26		
				97	14	36	0.45	0.15, 1.40		
	51–70 ^A	Colorectal cancer, age ≥65		48.2, median	34	55	1	Reference	0.34	
	≥71			66.8	36	61	0.97	0.50, 1.87		
				80	19	58	0.56	0.27, 1.15		
				97	27	54	0.83	0.39, 1.75		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
Tangrea 1997 ¹²⁷ ATBC [9242478]	19–50	Colorectal cancer (146 cases; 292 controls)	1–8	≤24.5	46	72	1	Reference	0.13	B
	51–70 ^A			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			
Women										
Wactawski-Wende 2006 ¹³¹ 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 ¹³⁰ NHS [15342452]	19–50	Colorectal cancer (192 cases; 384 controls)	1–11	40.2, median	53	77	1	Reference	0.02 ^C	B
	51–70 ^A			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 ¹²⁸ Japan PHC [17622244]	19–50	Colorectal cancer (179 cases; 358 controls)	1–13	<57.2	41	77	1	Reference	0.74	B
	51–70 ^A			57.2–69.0	34	73	1	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 ¹³³ WCC [329893]	19–50	Colon cancer (57 cases; 114 controls)	1–17	<43	nd	nd	1	Reference	0.57	C
	51–70 ^A			43.0–51.5	nd	nd	0.3	0.1, 1.0		
	≥71			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			

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
Garland 1989 ¹³² WCC [2572900]	19–50	Colon cancer (34 cases; 67 controls)	1–9	10 to <50	9	8	1	Reference	0.41	C
	51–70 ^A			50.0–67.5	7	13	0.48	0.13, 1.80		
	≥71			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 ¹²⁸ Japan PHC [17622244]	19–50	Colon cancer (141 cases; 282 controls)	1–13	<57.2	25	54	1	Reference	0.7	B
	51–70 ^A			57.2–69.0	27	55	0.98	0.48, 2.0		
	69.0–80.2			29	66	1	0.48, 2.3			
	≥80.2			38	62	1.2	0.51, 2.7			
Wu 2007 ¹²⁹ HPFS [17623801]	19–50	Colon cancer (139 cases; 276 controls)	1–9	48.3, median	49	66	1	Reference	0.005 ^D	B
	51–70 ^A			66.8	44	68	0.74	0.42, 1.33		
	≥71			80	17	68	0.29	0.14, 0.59*		
	97			29	74	0.46	0.24, 0.89*			
Tangrea 1997 ¹²⁷ ATBC [9242478]	19–50	Colon cancer (91 cases; 182 controls)	1–8	≤24.5	30	47	1	Reference	0.69 ^E	B
	51–70 ^A			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 ¹³⁰ NHS [15342452]	19–50	Colon cancer (148 cases; 296 controls)	1–11	41.2, median	41.2	75	1	Reference	0.17	B
	51–70 ^A			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	0.7	0.35, 1.38			

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
Otani 2007 ¹²⁸ Japan PHC [17622244]	19–50	Colon cancer (115 cases; 230 controls)	1–13	<57.2	21	53	1	Reference	0.12	B
	51–70 ^A			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 ¹²⁸ Japan PHC [17622244]	19–50	Rectal cancer (55 cases; 110 controls)	1–13	<57.2	18	20	1	Reference	0.06	B
	51–70 ^A			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 ¹²⁷ ATBC [9242478]	19–50	Rectal cancer (55 cases; 110 controls)	1–8	≤24.5	16	25	1	Reference	0.06 ^F	B
	51–70 ^A			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			
Wu 2007 ¹²⁹ HPFS [17623801]	19–50	Rectal cancer (40 cases; 80 controls)	1–9	53.0, median	11	30	1	Reference	0.08	B
	51–70 ^A			73.3	15	28	1.74	0.61, 5.00		
	≥71			93.5	14	22	3.32	0.87, 12.69		
Women										
Otani 2007 ¹²⁸ Japan PHC [17622244]	19–50	Rectal cancer (64 cases; 128 controls)	1–13	<57.2	20	24	1	Reference	0.17	B
	51–70 ^A			57.2–69.0	7	25	0.26	0.07, 1.0		
	69.0–80.2			17	30	0.46	0.15, 1.4			
	≥80.2			10	23	0.33	0.08, 1.3			
Feskanich 2004 ¹³⁰ NHS [15342452]	19–50	Rectal cancer (44 cases; 88 controls)	1–11	44.4, median	24	31	1	Reference	0.03	B
	51–70 ^A			66.2	10	26	92.4	10 0.8, 1.31		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
NEW Nested case-control studies										
Colorectal cancer										
Jenab 2010 ¹²³ European Prospective Investigation into Cancer and Nutrition (EPIC)	30–77 years	Colorectal Cancer (1248 cases;1248 controls)	NR	Quintile 1:<25	64	116	RR=1.32	0.87, 2.01	<0.001	B
				Quintile 2:25–50	473	873	1.28	1.05, 1.56		
				Quintile 3:50–75	448	909	1	Reference		
				Quintile 4:75–100	173	382	0.88	0.68, 1.13		
				Quintile 5:>100	90	216	0.77	0.56, 1.06		
Lee 2011 ¹²⁶ Physicians Health Study	40–84 years	Colorectal Cancer (229 cases;389 controls)	NR	Quartile 1 (median39.3 nmol/L)	57	153	1.00	Reference	0.67	B
				Quartile 2 (median 55.8 nmol/L)	41	138	0.71	0.42, 1.21		
				Quartile 3(median 66.8 nmol/L)	74	173	1.24	0.76, 2.04		
				Quartile 4(median 94.75 nmol/L)	57	154	1.08	0.62, 1.87		
Neuhouser 2012 ¹²⁴ WHI	50–79 years	Colorectal Cancer (1080 cases;1080 controls)	NR	<32.7	293	562	4.45	1.96, 10.10	0.003	A
				32.7–43.6	306	578	2.76	0.72, 3.14		
				43.6–64.5	250	520	1.51	1.30, 5.89		
				>64.5	231	500	1.00	Reference		
Woolcott 2010 ¹²⁵ multiethnic cohort	45–75 years	Colorectal Cancer (229 casea;434 controls)	NR	<42 nmol/L	67	154	1.00	Reference	0.010	A
				42.0–55.5 nmol/L	42	128	0.63	0.37, 1.08		
				55.5–65.8 nmol/L	38	126	0.54	0.32, 0.93		
				65.8–82.0 nmol/L	43	130	0.62	0.36, 1.07		
				≥82.0 nmol/L	39	125	0.60	0.33, 1.07		
				Per doubling	NR	NR	0.68	0.51, 0.92		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
Colon cancer										
Lee 2011 ¹²⁶ Physicians Health Study	40–84 years	Colon Cancer (136 cases;287 controls)	NR	Quartile 1 (median 39.25 nmol/L)	36	106	1.00	Reference	0.350	B
				Quartile 2 (median 55.75 nmol/L)	37	109	0.95	0.52, 1.74		
				Quartile 3 (median 66.8 nmol/L)	52	126	1.34	0.75, 2.39		
				Quartile 4 (median 94.75 nmol/L)	47	118	1.38	0.73, 2.64		
Jenab 2010 ¹²³	30–77 years	Colon Cancer (785 cases;785 controls)	NR	<25nmol/l	45	72	1.90	1.10, 3.29	<0.001	B
≥25<50nmol/l				300	549	1.36	1.05,1.76			
≥50<75nmol/l				286	581	1	Reference			
≥75<100nmol/l				104	242	0.86	0.62, 1.17			
European Prospective Investigation into Cancer and Nutrition (EPIC)				≥100nmol/l	50	126	0.71	0.46, 1.08		
Rectal cancer										
Jenab 2010 ¹²³	30–77 years	Rectal Cancer (463 cases, 463 controls)	NR	<25nmol/l	NR	NR	0.77	0.37, 1.59	0.320	B
European Prospective Investigation into Cancer and Nutrition (EPIC)				≥25<50nmol/l	NR	NR	1.17	0.84, 1.65		
				≥50<75nmol/l	NR	NR	1.00	Reference		
				≥75<100nmol/l	NR	NR	0.93	0.60, 1.45		
	≥100nmol/l	NR	NR	0.82	0.48, 1.40					
Lee 2011 ¹²⁶	40–84 years	Rectal Cancer (57 cases, 102 controls)	NR	Quartile 1 (median 39.3 nmol/L)	20	44	1.00	Reference	0.050	B
Physicians Health Study				Quartile 2 (median 55.8 nmol/L)	15	41	0.53	0.18, 1.60		
				Quartile 3 (median 66.8 nmol/L)	9	37	0.42	0.13, 1.40		
				Quartile 4 (median 94.8 nmol/L)	13	37	0.45	0.14, 1.46		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (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
Colon cancer										
NEW Cohort study										
Ordonez-Mena 2013 ⁹⁷ ESTHER		Colorectal Cancer	8 yrs	Q1	37	2373	HR 1.02	0.68, 1.53		B
				Q2+Q3	69	4741	HR 1.00	Reference		
				Q4	30	2368	HR 0.77	0.50, 1.20		

* Statistically significant (P<0.05).

^AMost representative life stage.

^BP for trend = 0.31 when cases diagnosed within 2 years of blood collection were excluded.

^CResults 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.

^DP for trend = 0.008 when cases diagnosed within 2 years of blood collection were excluded.

^EP for trend = 0.58 when cases diagnosed within 2 years of blood collection were excluded.

^FP 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

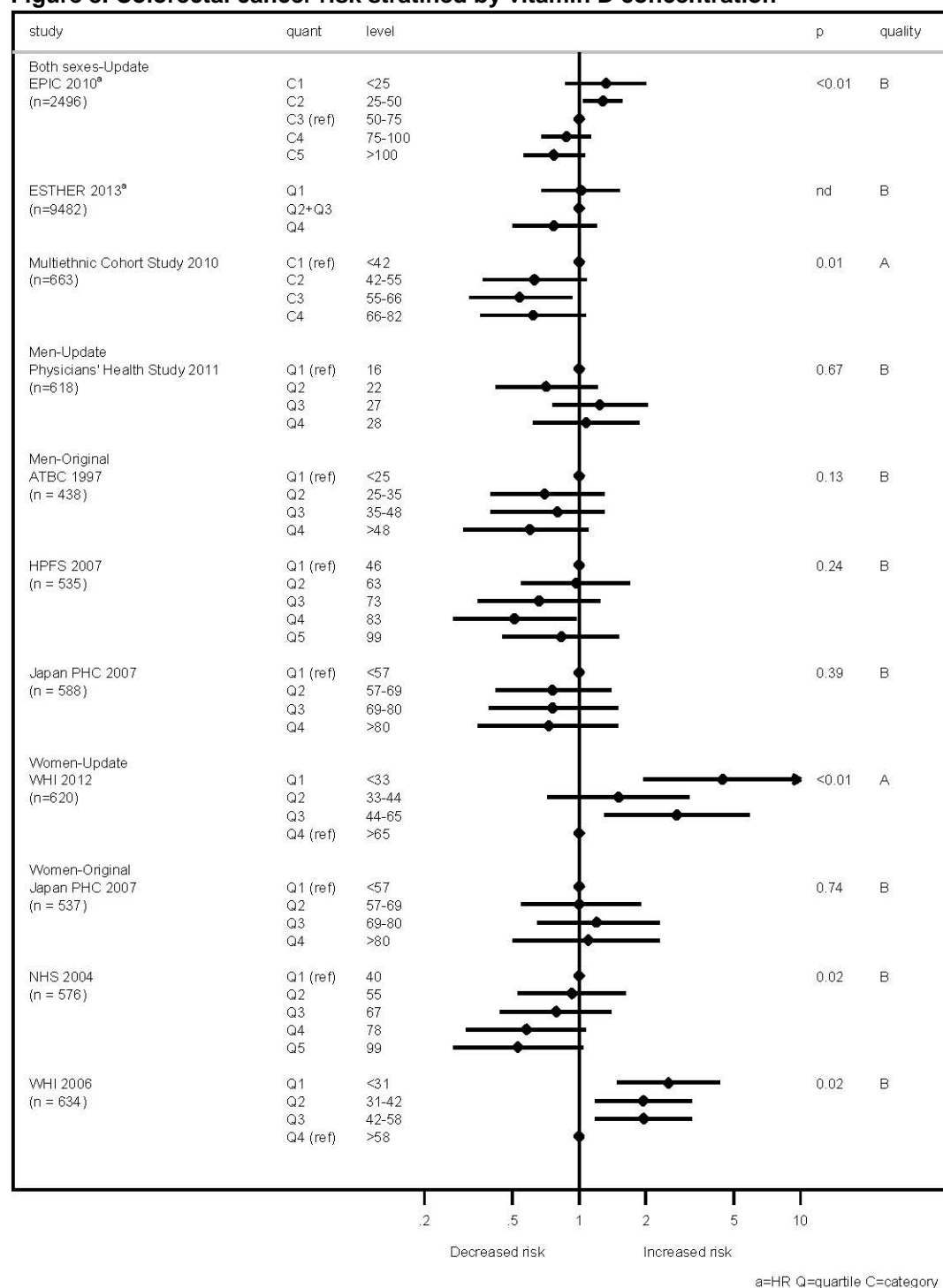


Figure 9. Colon cancer risk stratified by vitamin D concentration

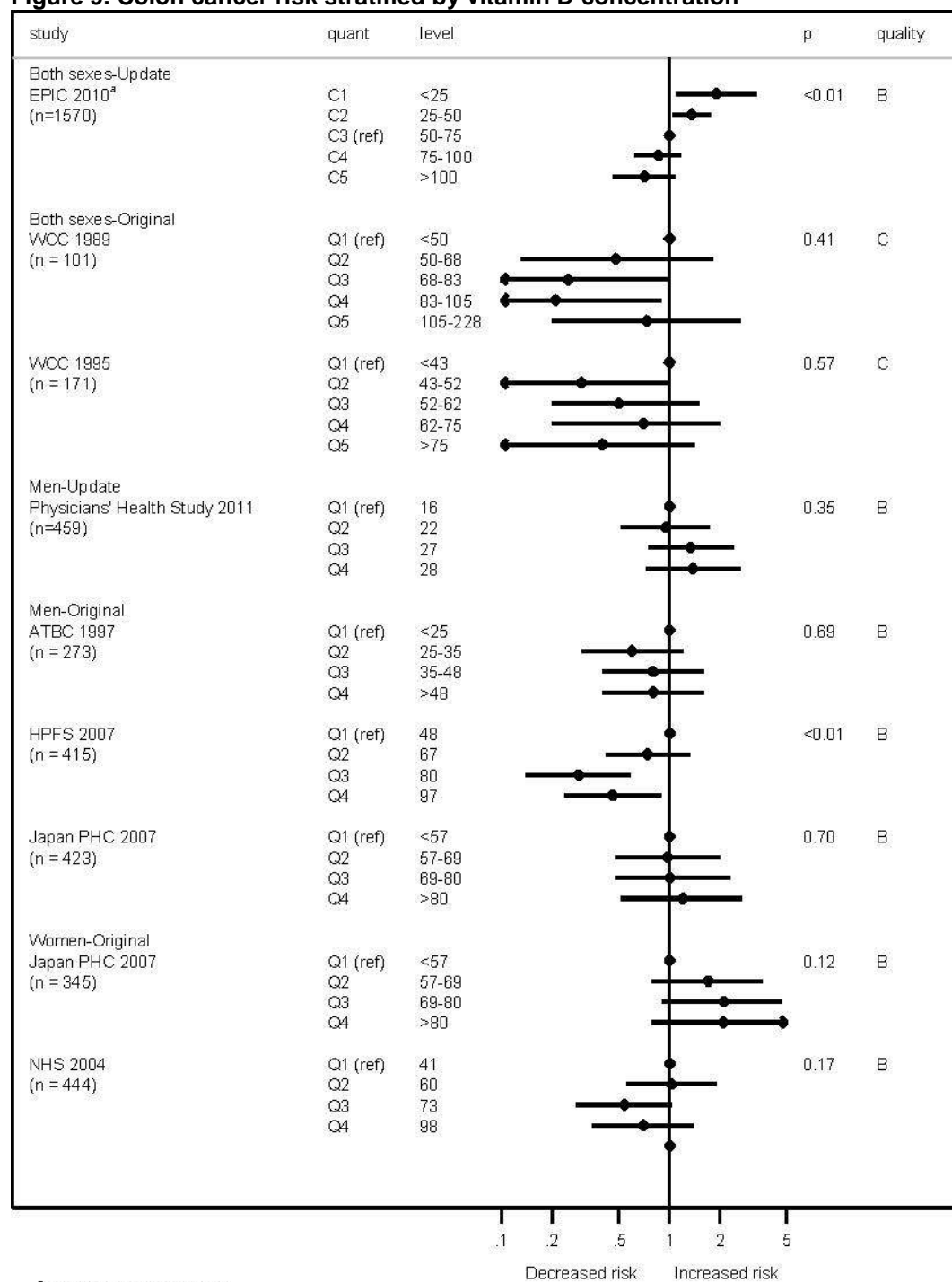
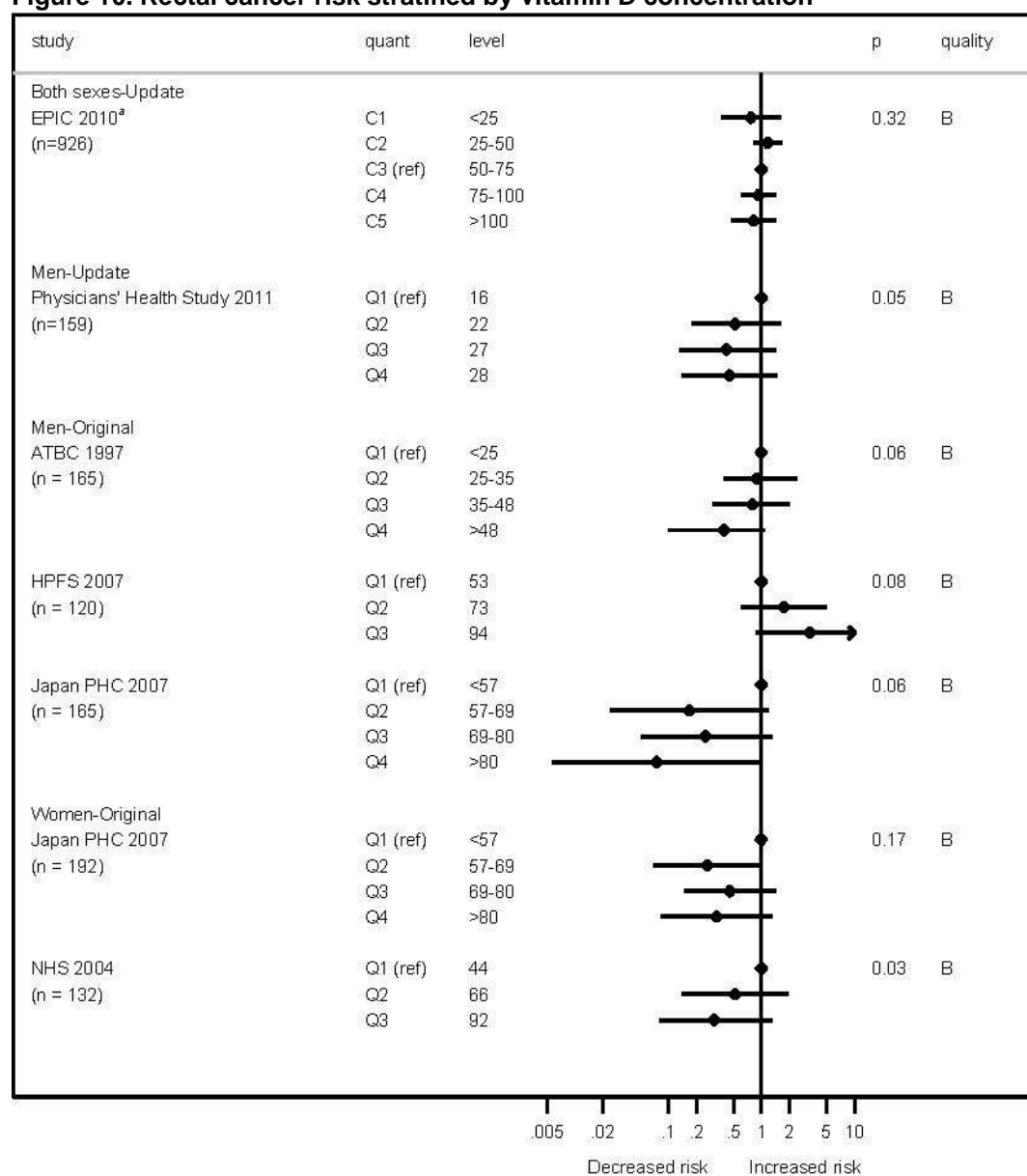


Figure 10. Rectal cancer risk stratified by vitamin D concentration



^a=HR C=Category Q=Quartile

Colorectal Adenoma

Synopsis

No **qualified** systematic reviews have evaluated the association between 25(OH)D concentrations and the risk of colorectal adenoma. **No new studies were identified for the update report. In the original report**, 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)

In the original report, one nested case-control study within the NHS evaluated the relationship between 25(OH)D concentrations and the risk of colorectal adenoma in women.¹³⁴ 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 [no new studies in the current report]

Studies in this Current Report							Confounders/Effect Modifiers Adjusted						Comments
Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle		
Nested Case-Control													
Platz 2000 ¹³⁴ 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 [no new studies in the current report]

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 ¹³⁴ NHS [11045788]	19–50 51– 70 ^A ≥71	Colorectal adenoma (326 cases; 326 controls)	5	16.3, median 22.6 28.3 38.0	103 62 61 100	82 80 82 82	1 0.64 0.58 1.04	Reference 0.41, 1.00 0.36, 0.95 0.66, 1.66	1.0	B
Colon adenoma										
Women										
Platz 2000 ¹³⁴ NHS [11045788]	19–50 51– 70 ^A ≥71	Colon adenoma (261 cases; 261 controls)	5	16.3, median 22.6 28.3 38.0	79 55 51 76	64 64 69 64	1 0.71 0.60 1.02	Reference 0.43, 1.18 0.35, 1.02 0.60, 1.73	1.0	B
Rectal adenoma										
Women										
Platz 2000 ¹³⁴ NHS [11045788]	19–50 51– 70 ^A ≥71	Rectal adenoma (65 cases; 65 controls)	5	16.3, median 22.6 28.3 38.0	24 7 10 24	18 16 13 18	1 0.38 0.34 1.59	Reference 0.12, 0.19 0.08, 1.42 0.50, 5.03	0.9	B

* Statistically significant (P<0.05)

^AMost 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 and the risk of breast cancer-specific mortality and found no association. Eight observational studies that assessed the association between 25(OH)D and breast cancer were identified for the current report. Two cohort and four nested case-control studies found no association.**^{124,135-137} **Two nested case-control studies found increasing risk of breast cancer with decreasing 25(OH) concentrations.**^{138,139}

Two studies that examined the relationship between vitamin D and calcium intake or 25(OH)D and breast density were identified. A RCT found a decrease in percent mammographic density among women who had ≥ 400 IU/d total vitamin D intake.¹⁴⁰ A nested case-control found lower risk of increased mammographic density with 25(OH) concentrations above the first quartile.¹⁴¹

In the original report, one cohort study compared serum 25(OH)D concentrations and the risk of breast cancer-specific mortality,¹⁰³ and two nested case-control studies compared 25(OH)D concentrations and the risk of breast cancer.^{142,143} The cohort study utilizing NHANES III data found significant decrease in breast cancer-specific mortality during 9 years of follow up 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 follow up.^{142,143} All three studies were rated B quality.

Detailed Presentation (Tables 26a-d & 27a-d)

Nine observational studies that assessed the association between 25(OH)D and breast cancer incidence were identified for the current report. One observational study that assessed the association between 25(OH)D and breast cancer-specific mortality was also identified.

Two cohort studies, within the Women's Healthy Eating and Living (WHEL) Study and the Nurses' Health Study II (NHSII) and the ESTHER study, found no association between 25(OH)D and breast cancer (all rated B).^{97,144} The study in the WHEL cohort also found no association after stratifying by pre- and post-menopause. The Health, Eating, Activity, and Lifestyle (HEAL) cohort study found no association between 25(OH)D and breast cancer-specific mortality (rated B).

Six nested case-control studies were identified. Four of the nested case-control studies found no association between 25(OH)D concentrations and breast cancer incidence (rated 3A, 1B).^{124,136,137} The other two nested case-control studies found increasing risk of breast cancer with decreasing 25(OH) concentrations (both rated B).^{138,139} In one of these, a stratified analysis by menopause status found the negative trend remained for premenopausal women but not for postmenopausal women.¹³⁹

Two studies with breast density outcomes were identified. The Women's Health Initiative (WHI) Mammogram Density Ancillary Study found a decrease in percent mammographic density among women who had ≥ 400 IU/d total vitamin D intake and were

enrolled in the vitamin D₃ 400 IU + 1,000 mg calcium per day arm of the trial.¹⁴⁰ A nested case-control study within the Nurses' Health Study found lower percent mammographic density in women who had 25(OH)D levels above the first quartile; statistical significance was not assessed.¹⁴¹

From the original report, 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).¹⁰³ The study included 71% non-Hispanic white, 14% non-Hispanic black, 6% Mexican American, and 9% from other races. During 9 years of follow up, 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% CI 0.08–0.93). The breast cancer-specific mortality was one of many cancer-specific mortality outcomes reported in this study.

In the original report, 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.^{142,143} 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 37.5 nmol/L compared with higher levels was 0.81 (95% CI 0.59, 1.12).¹⁴³

Findings by Age and Sex

In the original report, in the one nested case-control study (methodological quality B) including both premenopausal and postmenopausal women, no relationship was found between serum 25(OH)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**

In the NHSII cohort study, 25(OH)D concentration from women aged 32–54 years was not associated with breast cancer incidence. In the original report, a follow up 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**
The ESTHER study found no association between serum 25(OH)D concentration and breast cancer incidence in women aged 50–74 years. The WHI Mammogram Density Ancillary Study found an association between vitamin D intake and percent mammographic density in women aged 50 to 79 who had ≥400 IU/d total vitamin D

intake.¹⁴⁰ The nested case-control studies identified for the update report included individuals with mean age ranged from 57 to 65 years. A trend between higher 25(OH)D levels and lower risk of breast cancer was found in two studies; the other two studies found no association. In the original report, 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**
In the WHEL cohort study, no significant trends were found between 25(OH)D and breast cancer in pre- and post-menopausal women.¹⁴⁴ In a nested case-control study, no association was found between breast cancer risk and 25(OH)D in postmenopausal women.¹³⁹
- **Pregnant & lactating women**
Not reviewed

Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report)

From Original Report						Confounders/Effect Modifiers Adjusted				Comments		
Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons		Demograph		Medical		Lifestyle			
Nested Case-Control												
Bertone-Johnson 2005 ¹⁴² NHS US (38° N) [16103450]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y	No Cancer 57 (7.0)	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA All year	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X		X		X	
Freedman 2008 ¹⁴³ PLCO Trial US (38° N) [18381472]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y	No Cancer 67 (ND)	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA Dec-Sep	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X		X		X	
NEW Studies												
Nested Case-Control												
Neuhouser 2012 ¹²⁴ WHI US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y	Post-menopausal 65.1 (SD 6.8)					X				X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset

Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report) (continued)

				Confounders/Effect Modifiers Adjusted							
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Comments
Nested Case-Control											
Almquist, 2010 ¹³⁷ Malmo Diet and Cancer Study	• Health outcome • Mean age (SD), y	Healthy 57 (SD 7.3)		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Engel, 2010 ¹³⁸ French E3N France	• Health outcome • Mean age (SD), y	nd 56.9 (6.4)		Breast cancer risks: Quintile 1 vs. Quintile 2, 3		X	X				
McCullough, 2009 ¹³⁶ Cancer Prevention Study-II (CPS-II)	• Health outcome • Mean age (SD), y	nd 69.6 (5.8)		Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X		
Rejnmark, 2009 ¹³⁹ Denmark	• Health outcome • Mean age (SD), y	nd 58 (29–87)		Breast cancer risks: Tertile 1 vs. Tertile 2, 3							
NEW Cohort study											
Kuhn 2013 ¹⁴⁵ EPIC Multiple Countries	• Health outcome • Mean age (SD), y	Nd 50.7 (SD 8.8)		Breast Cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X	X	This analysis does not include data from the Malmo site, as these data were analyzed and published separately as Almquist, 2010, reference 126 in the original report.

Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report)

				Confounders/Effect Modifiers Adjusted							
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Comments
Freedman 2007 ¹⁰³ NHANES III US (38° N) [17971526]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y	Non-institutionalized 44 (ND)		Breast cancer risks: Quintile 1 vs. Quintile 2	X	X	X		X	X	
NEW Studies											
Jacobs, 2011 ¹⁴⁴ Women's Healthy Eating and Living (WHEL) US (various)	<ul style="list-style-type: none">• Health outcome• Mean age (SD), y• Male (%)	Cancer in remission 51.9 (SD 9) 0%		Breast cancer risks: Quartile 4 vs. Quartile 1, 2, 3							This article contains both prospective cohort and case-control data. Case-control data given here
Eliassen, 2011 ¹³⁵ NHSIII	<ul style="list-style-type: none">• Health outcome• Mean age (SD), y• Male (%)	nd 44.9 (SD 4.4) 0%		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
NEW Cohort study											
Ordonez-Mena 2013 ⁹⁷ ESTHER Saarland, Germany	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	nd NR (50–74) 54%		Breast cancer risk: Tertile 2 vs. Tertile 1 and 3		X	X			X	confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

Table 26c. Vitamin D and breast density: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted							Comments
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure	Lifestyle	
New Studies											
Bertone-Johnson, 2012 ¹⁴⁰ WHI Mammogram Density/Ancillary Study US	<ul style="list-style-type: none">Health outcomeMean age 62 (SD 8) (SD), yMale (%) 0%	Post-menopausal	Percent mammographic density stratified by 25(OH)D ₃ medians								

Table 26d Vitamin D and breast density: Characteristics of nested case-control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted							Comments
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure	Lifestyle	
New Studies											
Green 2010 ¹⁴¹	<ul style="list-style-type: none">Health outcomeMean age 61 (nd) (SD), yMale (%) 0%	Post-menopausal	Percent mammographic density stratified by 25(OH)D ₃ quartiles								

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report)

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
Bertone- Johnson 2005 ¹⁴² NHS [16103450]	Pre- and Post- menopausal	Breast cancer (701/1425)	<1–82 mo	25(OH)D	≤50 (1 st batch)	159	297	1	Reference	nd	B
					≤70 (2 nd batch)						
					≤45 (3 rd batch)						
					51–70	149	278	0.95	0.66, 1.36		
					72–85						
					47 to 60						
					72–82	125	266	0.74	0.51, 1.06		
					87–97						
					62–72						
					85–97	144	296	0.8	0.58, 1.11		
					100–117						
					75–90						
					≥100	124	265	0.73	0.49, 1.07		
					≥120						
					≥92						
		Breast cancer <60 y (701/1425)				97	191	1	Reference	NS	
						84	170	0.96	0.62, 1.49		
						77	164	0.8	0.51, 1.26		
						90	192	0.85	0.55, 1.32		
						70	146	0.92	0.57, 1.48		

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report) (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 ¹⁴³ PLCO Cancer Screening Trial [18381472]	Pre- and Post- menopausal	Breast cancer ≥60 y (701/1425)	12 y	25(OH)D		62	109	1	Reference	0.03	B	
						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			
					Breast cancer (1005/2010)	<46	172	2010	1	Reference		NS
		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			
NEW Studies												
Neuhouser 2012 ¹²⁴ WHI	50–79 years	Breast Cancer (1080 cases, 1080 controls)	NR	25(OH)D	<36.7	105	181	1.06	0.78, 1.43	0.60	A	
					36.7 to <50.9	68	147	1.11	0.83, 1.49			
					50.9 to <64.9	84	162	0.99	0.75, 1.31			
					>64.9	53	130	1.00	Reference			
Almquist 2010 ¹³⁷ Malmo Diet and Cancer Study	Born 1923–1950	Breast Cancer (213 cases, 213 controls)	7.0 years	25(OH)D3	Quartile 1(<70)	NR	213	OR=1.00	Reference	0.71	A	
					Quartile 2 (71–86)	NR	164	0.84	0.60, 1.15			
					Quartile 3(87– 105)	NR	176	0.84	0.60, 1.17			
					Quartile 4(>105)	NR	192	0.93	0.66, 1.33			
			7.0 years	25(OH)D2+D3	Quartile 1(72)	NR	191	1.00	Reference			
					Quartile 2 (72–87)	NR	170	0.95	0.68, 1.31			
					Quartile 3(88– 106)	NR	183	0.94	0.68, 1.32			
					Quartile 4(>106)	NR	191	0.96	0.68, 1.37			
Engel 2010 ¹³⁸ French E3N	born between 1925 and 1950	Breast Cancer (636 cases, 1272 controls)	≤10 years	25(OH)D	<49.5 nmol/L	226	630	OR=1.00	Reference	0.02	A	
					49.5–67.5 nmol/L	198	600	0.81	0.63, 1.04			
					>67.5 nmol/L	191	603	0.73	0.55, 0.96			

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report) (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			
McCullough 2009 ¹³⁶ Cancer Prevention Study-II (CPS- II)	47–85 years	Breast Cancer(516 cases, 516 controls)	1month–6.9 years	25(OH)D	<36.7	89	193	OR=1.00	Reference					
					36.7–49.7	115	217	1.29	0.86, 1.94					
					49.8–60.7	99	204	1.14	0.75, 1.72		A			
					60.8–73.1	118	220	1.44	0.96, 2.18					
					>73.1	95	198	1.09	0.70, 1.68	0.60				
Rejnmark 2009 ¹³⁹	Pre- and Post- menopausal	Breast Cancer(142 cases, 420 controls)	NR	25(OH)D	<60nmol/L	NR	NR	1.00	Reference					
					60–84nmol/L	NR	NR	0.94	0.59, 1.47					
					>84nmol/L	NR	NR	0.52	0.32, 0.85	<0.05				
	Premenopausal				<60nmol/L	NR	NR	1.00	Reference					
					60–84nmol/L	NR	NR	0.59	0.26, 1.33					
					>84nmol/L	NR	NR	0.38	0.15, 0.97	<0.05				
	Postmenopausal				<60nmol/L	NR	NR	1.00	Reference					
					60–84nmol/L	NR	NR	1.20	0.67, 2.16					
Kuhn 2013 ¹⁴⁵	40–65 years	Breast Cancer	4.1 yrs	25(OH)D	>84nmol/L	NR	NR	0.71	0.38, 1.30	>0.05				
					Q1: <=39.3	342	688	1.00	Reference	0.67				
					Q2: 39.4–50.9	357	707	1.03	0.83, 1.29					
					Q3: 51.0–63.0	324	670	0.94	0.74, 1.19					
					Q4: >63.0	368	717	1.07	0.85, 1.36		A			
EPIC					log2 (continuous)	1391	2782	1.01	0.86, 1.19	0.86				

* Statistically significant (P<0.05)

^A Total number of women not reported

Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report)

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 2007 ¹⁰³ NHANES III [17971526]	All Adults	Breast cancer mortality (28/ND) ^A	105 mo	25(OH)D	<63 ≥63	20 8	ND ND	1 HR 0.28	Reference 0.08, 0.93*	NS	B
NEW Studies											
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living (WHEL)		Breast Cancer (512/3085)	NR	25(OH)D	<25 nmol/L (deficient)	nr	51	OR=1.14	0.57, 2.31		
					≥25 and <50 nmol/L (insufficient)	nr	282	1.00	0.68, 1.48		
					≥50 and <75 nmol/L (suboptimal)	nr	410	1.05	0.76, 1.47		
					≥75 nmol/L (optimal)	nr	281	1.00	Reference	0.85	
		Premenopausal			<25 nmol/L (deficient)	nr	6	0.17	0.01, 4.56		
					≥25 and <50 nmol/L (insufficient)	nr	31	1.02	0.33, 3.16		B
					≥50 and <75 nmol/L (suboptimal)	nr	45	1.76	0.64, 4.87		
					≥75 nmol/L (optimal)	nr	36	1.00	Reference	0.61	
		Postmenopausal			<25 nmol/L (deficient)	nr	37	1.45	0.62, 3.37		
					≥25 and <50 nmol/L (insufficient)	nr	202	1.09	0.68, 1.76		
					≥50 and <75 nmol/L (suboptimal)	nr	266	0.90	0.60, 1.36		
					≥75 nmol/L (optimal)	nr	187	1.00	Reference	0.49	
Eliassen 2011 ¹³⁵ NHSIII		Breast Cancer (613 cases, 1218 controls)	NR	25(OH)D	Quartile 1 (<46 nmol/L)	141	441	1.00	Reference		
					Quartile 2 (46.0 to 61.5 nmol/L)	151	456	1.05	0.79, 1.39		
					Quartile 3 (61.5 to <76.5 nmol/L)	145	452	0.95	0.71, 1.29		A
					Quartile 4 (≥76.5 nmol/L)	176	482	1.20	0.88, 1.63	0.320	
Ordonez- Mena 2013 ⁹⁷ ESTHER	50–74 years	Breast Cancer	8 yrs	25(OH)D	Q1	38	1464	1.08	0.72, 1.60		
					Q2+Q3	71	2951	1.00	Reference		B
					Q4	26	846	1.39	0.89, 2.18		

^ATotal number of women not reported

Table 27c. Vitamin D and breast density: Results of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	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
Bertone- Johnson, 2012 ¹⁴⁰ WHI Mammogram Density/Ancillary Study	50–79 years	percent mammographic density	1°	1 yr	(Vit D ₃ 400 IU+1,000 mg calcium)/day	179	%	3.7	final=3.6	2.9, 4.6	+0.8	-0.2, 1.8	0.1	A
					placebo	151	%	2.8	final=2.8	2.2, 3.7				
	Total vitamin D intake <200				(Vit D ₃ 400 IU+1,000 mg calcium)/day	87	%	3.6	final=3.5	2.5, 4.9	+0.5	-0.9, 1.9	0.47	
					placebo	77	%	3	final=3	2.1, 4.3				
	Total vitamin D intake >400				(Vit D ₃ 400 IU+1,000 mg calcium)/day	53	%	4.3	final=4	2.6, 6.0	+1.7	-0.1, 3.5	0.07	
					placebo	44	%	2.7	final=2.3	1.3, 4.2				
	Total vitamin D intake 200– <400				(Vit D ₃ 400 IU+1,000 mg calcium)/day	29	%	2.4	final=2.8	1.4, 5.6	-0.4	-2.5, 1.7	0.70	
					placebo	24	%	2.5	final=3.2	1.7, 6.1				

Note: Outcomes cells are shaded for the Control rows.

Table 27d. Vitamin D and breast density: Results of nested case-control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	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
Green 2010 ¹⁴¹														
Nurses' Health Study		percent mammogram- phic density	1°	within one year of blood collection	1,25(OH) ₂ D: 1st quartile (32.5– 72.8 nmol/l)	110	%	nr	Final=25.2					B
					1,25(OH) ₂ D: 2nd quartile (72.8 –82.8 nmol/l)	108	%	nr	27.6		+2.1	nc		
					1,25(OH) ₂ D: 3rd quartile (82.8–93.3 nmol/l)	110	%	nr	23.3		-2.2	nc		
					1,25(OH) ₂ D: 4th quartile (93.5-140.5 nmol/l)	114	%	nr	25.8		+0.3	nc		
					25(OH)D: 1st quartile (cut points vary by batches)	118	%	nr	26.3					
					25(OH)D: 2nd quartile	115	%	nr	25.6		-0.7	nc		
					25(OH)D: 3rd quartile	124	%	nr	24.8		-1.5	nc		
					25(OH)D: 4th quartile	112	%	nr	25.7		-0.6	nc		

Pancreatic Cancer

Synopsis

No qualified systematic reviews evaluated associations between serum 25(OH)D concentrations and the incidence of pancreatic cancer. **A pooled nested case-control study within eight cohorts found an association between 25(OH)D concentration and pancreatic cancer (rated A).**¹⁴⁶ Individuals with 25(OH)D concentration ≥ 100 nmol/L had greater risk of pancreatic cancer incidence compared to those with 25(OH)D < 25 nmol/L (OR=2.24, 95% CI 1.22, 4.12).

In the original report, 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

The pooled nested case-control study is based on 8 cohorts: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), CLUE, the Cancer Prevention Study II Nutrition Cohort (CPSII), the New York University Women's Health Study (NYU-WHS), the Multiethnic Cohort Study (MEC), the PLCO, and the Shanghai Women's and Men's Health Studies (SWHS and SMHS)¹⁴⁶. The pooled sample contains 952 cases (median age 62, IQR 56–68) and 1,333 controls (median age 52, IQR 57–67). Serum 25(OH)D concentration was stratified into sextiles. The odds ratio for pancreatic cancer was 2.24 (95% CI 1.22, 4.12) comparing the 6th sextile (≥ 100 nmol/L) to the 1st sextile (< 25 nmol/L). The result was adjusted for age, race/ethnicity, sex, cohort, date of blood draw, BMI, smoking status, and diabetes status.

In the original report, 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.¹⁴⁷ 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% 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.

In the original report, 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.¹⁴⁸ 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% 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% 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 pooled nested case-control study within eight cohorts found that individuals with 25(OH)D concentration ≥ 100 nmol/L had greater risk of pancreatic cancer incidence compared to those with 25(OH)D <25 nmol/L (OR=2.24, 95% CI 1.22, 4.12). In the original report, 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 (5th vs. 1st quintile, >65.5 vs. <32 nmol/L: OR 2.92, 95% 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 (5th vs. 1st quintile, >82.3 vs. <45.9 nmol/L: OR 1.45, 95% 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 (4th vs. 1st quartile >78.4 vs. <49.3 nmol/L: OR=4.03; 95% 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 (updated from original report)

Author Year Trial/Cohort Country (Latitude) [PMID]	Population	25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Stolzenberg-Solomon 2006 ¹⁴⁷ 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 ¹⁴⁸ 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	
NEW Studies											
Stolzenberg-Solomon, 2010 ¹⁴⁶ Cohort Consortium Vitamin D Pooling Project or Rarer Cancers	Health status Mean age (SD), y Male (%)	nd nd (nd) 66.5%			Pancreatic risk stratified by baseline 25(OH)D sextiles						
Afzal 2013 ⁹⁹ Denmark	Health status Mean age (SD), y Male (%)	NR 58 (47–65) 45%			Pancreatic risk stratified by baseline 25(OH)D category		X	X		X	HR (95%CI) for pancreatic cancer are shown in Figure 1

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report)

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 ¹⁴⁷ 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	1.3	0.70, 2.40		
				41.1–51.1	47	80	2.12	1.15, 3.90*		
				51.1–65.5	35	81	1.5	0.81, 2.76		
				>65.5	57	79	2.92	1.56, 5.48*		
Stolzenberg- Solomon 2009 ¹⁴⁸ 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		

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report) (continued)

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
NEW Studies										
Stolzenberg– Solomon 2010 ¹⁴⁶ Cohort Consortium Vitamin D Pooling Project or Rarer Cancers		Pancreatic Cancer (952 cases, 1333 controls)	nd	<25	115	256	1.00	Reference	0.14	A
				25 to <37.5	164	389	1.04	0.74, 1.44		
				37.5 to <50.0	208	494	1.10	0.79, 1.55		
				50.0 to <75.0	306	764	1.06	0.76, 1.48		
				75.0 to <100.0	120	310	1.08	0.73, 1.59		
				>100	39	69	2.24	1.22, 4.12		
Afzal 2013 ⁹⁹		Pancreatic Cancer	28 yrs	25(OH)D, 50% reduction in plasma levels	109	9791	HR 1.05	0.84, 1.30		B

* 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

The current report identified five RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and three cohort studies that assessed the association between vitamin D concentrations and risk for infectious illnesses. RCTs of infants and adults reported no significant effect of supplementation on the risk for upper respiratory infections; whereas one RCT conducted among 4-year-old Japanese children reported a positive effect of supplementation. Three prospective cohort studies observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory infections at 3 to 6 months of age, in New Zealand, South Korea, and the Netherlands. A Norwegian prospective study found an association between lower midpregnancy serum 25(OH)D and lower respiratory tract infections in the first 36 months of life. Two studies of school-age children, one in Colombia and one in Canada, observed associations between low serum 25A(OH)D and gastrointestinal tract infections and ear infections, and viral respiratory tract infections, respectively. A study of healthy U.S. adults found an association between serum concentrations of 25(OH)D levels of 95nmol/L or higher and reduced risk for acute respiratory viral infections. Studies of German and Finnish adults observed associations between lower serum 25(OH)D and respiratory disease mortality and pneumonia, respectively.

The current report identified one RCT that found no effect of prenatal vitamin D supplementation on the risk for wheeze, atopy, or eczema at 3 years of age. The report also identified five prospective cohort/nested case control studies that reported mixed associations of serum concentrations of 25(OH)D and risk for asthma, atopy, and/or eczema. An Australian study observed a significant association of cord blood 25(OH)D and risk for eczema but not allergies at 12 months of age. A prospective cohort study conducted in the UK found no association between maternal serum 25(OH)D at 34 weeks gestation and asthma, wheeze, and atopy in their children at 6 years of age. A prospective cohort study conducted in the Netherlands found that serum 25(OH)D concentrations at 4 years of age significantly predicted asthma and severe asthma at 8 years of age. Another UK longitudinal study found a small but significant association of wheeze and antecubital dermatitis in 10-year old children with serum levels of 25(OH)D₂ but a negative association with 25(OH)D₃. Finally, the HUNT study, a large population health survey in Norway, found no association of 25(OH)D with asthma in women and only a weak association in men that disappeared when adjusted for confounders.

The current report identified one RCT and four prospective cohort studies on the risk for autoimmune disease. A substudy of the WHI CaD trial found no effect of supplementation on women's risk for rheumatoid arthritis. Two nested case control studies and one cohort study assessed the association between maternal serum 25(OH)D concentrations or subsequent childhood or adult status with risk for type 1 diabetes mellitus and reported mixed findings. One study assessed the effects of maternal 25(OH)D concentrations on the risk for multiple sclerosis (MS) in the offspring and also assessed the

effect of 25(OH)D concentrations across the adult population on the risk for subsequent MS and found mixed effects.

In the original report, analyses using NHANES III data (general adult populations living in the United States) 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 30a-d & 31a-d)

Infection. The current report identified five RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and nine cohort studies that assessed the association between 25(OH)D concentrations and risk for infectious illnesses.

A RCT in Afghanistan that randomized infants to 100,000IU every 3 months for 18 months or to placebo found no effect of supplementation on the incidence of pneumonia or subsequent episodes of pneumonia (rated A).¹⁴⁹ A U.S. RCT that randomized healthy adults 18 to 80 years of age to 2000IU vitamin D per day or placebo for 3 months reported no effect of supplementation on the incidence or duration of upper respiratory infections (rated B).¹⁵⁰ A Finnish study that randomized male soldiers, 18 to 28 years of age, to 400IU vitamin D per day or placebo for 6 months reported no effect on the acute prevalence of respiratory infection or self-reported cold symptoms but a small significant effect on the number of soldiers who had no days absent from duty (adjusted OR 1.89 [1.01, 3.54](rated B).¹⁵¹ The VIDARIS Study, a New Zealand RCT of 322 adults 18 years of age and older (mean age 47, 25% men) that randomized individuals to an initial 200,000 IU oral dose of vitamin D₃, then 200,000 IU 1 month later, then 100,000 IU monthly or placebo for 18 months found no effect on the number of upper respiratory infections, days of work missed, or duration of symptoms (rated A).¹⁵²

Nine prospective cohort studies were also identified for the current report that assessed the association of prenatal or baseline 25(OH)D concentrations with risk for infectious illness incidence or mortality.

A prospective cohort study in the Netherlands followed 156 infants from birth to 6 months of age and observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory syncytial virus bronchiolitis infections (rated B).¹⁵³ A prospective cohort study in New Zealand followed a group of infants from birth and found an association of low cord blood serum 25(OH)D status with increased risk for respiratory infection at 3 months of age (rated B).¹⁵⁴ A study in South Korea (the COCOA study) followed 525 newborns from birth to 6 months of age and found an association between low maternal cord blood 25(OH)D concentrations and increased risk for viral respiratory tract infections (p=0.0004) (rated B).¹⁵⁵ A Norwegian prospective cohort study (MoBa) followed 1248 infants from birth to 36 months and observed an association between increasing midpregnancy maternal 25(OH)D concentrations and decreasing frequency and number of lower respiratory tract infections (rated B).¹⁵⁶

A prospective cohort study of 475 school-age children, the Bogota School Children Cohort, observed an association between lower baseline serum 25(OH)D and increased risk for gastrointestinal tract infections (RR 2.05) and ear infections (RR 2.36) (rated B).¹⁵⁷ A

prospective cohort study in Canadian Hutterite communities followed 743 children 3 to 15 years of age for 6 months and found that younger age and lower serum 25(OH)D levels were associated with increased risk for viral RTI: Serum 25(OH)D levels <75 nmol/L increased the risk of viral RTI by 50% (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.10–2.07, P=.011) and levels <50 nmol/L increased the risk by 70% (HR, 1.67; 95% CI, 1.16–2.40, P=.006).¹⁵⁸

A study of healthy U.S. adults followed for 4 months found an association between serum concentrations of 25(OH)D levels of 95nmol/L or higher and reduced risk for acute respiratory viral infections (rated A).¹⁵⁹ The ESTHER Study of 9,578 German adults observed an association between vitamin D deficiency (defined by the authors as less than 30nmol/L) and an increased risk for respiratory disease mortality (HR2.50, 1.12, 5.56) (rated B).⁷⁶ The Kuipio IHD Risk Factor Study, which followed 1,421 Finnish adults 53 to 73 years of age for 10 years, found a 2.6-fold increased risk for pneumonia in the lowest compared with the highest tertile of serum 25(OH)D (rated B).¹⁶⁰

Asthma, Atopy, and Eczema. The current report identified one RCT and five prospective studies on the association between serum 25(OH)D and risk for asthma, atopy, and/or eczema. A UK RCT randomized 180 pregnant women at 27 weeks gestation to receive 0 or 800IU vitamin D daily for the remainder of pregnancy or one oral bolus of 20,000IU; at 3 years of age, no significant differences were seen among 158 offspring in their risk for ever having experienced wheeze, atopy, or eczema (rated A).¹⁶¹

An Australian cohort study measured maternal and cord blood and found a significant association between cord blood 25(OH)D and decreased risk for eczema at 12 months of age. No association was seen with the results of skin prick tests for environmental and food allergies and IgE testing for food allergy.¹⁶²

A UK prospective study that followed 860 mother-infant pairs found no association between maternal serum 25(OH)D at 34 weeks gestation and the incidence of asthma, wheeze, or atopy at 6 years of age.¹⁶³

A longitudinal study in the Netherlands (PIAMA) is assessing associations of nutritional indicators with the risk for asthma in a large birth cohort. The most recent data suggest that rates of asthma and severe asthma at 8 years of age are higher among those whose serum 25(OH)D concentrations were in the lowest or middle tertile at 4 years of age.¹⁶⁴

The Avon Longitudinal Study of Parents and Children, a UK study, measured serum 25(OH)D2 and D3 (using HPLC/ tandem mass spectrometry) in some 14,500 children and found an association between lower levels of 25(OH)D2 at a mean age of 9.8 years and higher levels of wheeze, poor lung function, and flexural (antecubital) dermatitis at a mean age of 15.5 years; higher levels of 25(OH)D3 were associated with increased incidence of flexural dermatitis and wheezing but were not associated with lung function. Although the authors adjusted for confounders, they cautioned about interpreting the results without conducting trials.¹⁶⁵

The HUNT study analyzed the association of baseline vitamin D (and other nutrient) status in adults with the risk for asthma 11 years later using data from a large-scale longitudinal survey of health in Norway. They found no association of 25(OH)D concentrations with subsequent risk for asthma among women and a small association in men that disappeared after adjustment for confounders.¹⁶⁶

Autoimmune. The current report identified one RCT, three nested case control studies, and one prospective cohort study on the risk for autoimmune disease. A substudy of the

WHI CaD trial that assessed participants at 5.1 years found no effect of supplementation with 400IU vitamin D and 1000mg calcium on women's risk for rheumatoid arthritis (rated A).¹⁶⁷ A nested case control study among U.S. Navy and Marine Corps military personnel observed an association of Type 1 diabetes mellitus (DM) with serum 25(OH)D status at enlistment (310 cases and 310 matched controls) among white soldiers but not among black or Hispanic soldiers (rated B).¹⁶⁸ A nested case control study conducted in Norway observed a trend toward an increasing association of type 1 DM in the first 15 years of life and decreased maternal 25(OH)D concentrations (rated C).¹⁶⁹ A U.S. prospective cohort study of children at increased risk for developing Type 1 DM based on an Islet Autoimmune genetic marker, found no association of 25(OH)D concentrations at 9 months of age and subsequent risk for progression to DM (rated B). GRoMS, a nested case control study among individuals in Sweden who developed multiple sclerosis, found no association with maternal serum 25(OH)D concentrations but a possible association of adult levels with subsequent risk for the disease (rated B).¹⁷⁰

In the original report, one study analyzed NHANES III data and showed no association between baseline 25(OH)D concentrations and infectious disease.⁸⁵ 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.⁵⁵ 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 in original study. A RCT in Afghanistan that randomized infants to 100,000IU every 3 months for 18 months or to placebo found no effect of supplementation on the incidence of pneumonia or subsequent episodes of pneumonia. A prospective cohort study in South Korea that followed 525 infants from birth to 6 months of age observed a significant association of low cord blood 25(OH)D and increased risk for respiratory tract infection. A prospective cohort study in the Netherlands followed 156 infants from birth to 6 months of age and observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory syncytial virus bronchiolitis infections. A prospective cohort study in New Zealand followed a group of infants from birth and found an association of low cord blood serum 25(OH)D concentrations with increased risk for respiratory infection at 3 months of age.

- **7 mo–2 y**

No data in original study. A RCT in the UK that randomized pregnant women at 27 weeks gestation to receive 0 or 800IU vitamin D daily for the remainder of pregnancy or one oral bolus of 20,000IU; at 3 years of age, no significant differences were seen among 158 offspring in their risk for ever having experienced wheeze, atopy, or eczema. A prospective cohort study in Norway that followed 1,248 children from birth to 36 months of age observed a significant association between maternal serum 25(OH)D at midpregnancy and the number and frequency of lower

respiratory tract infections. An Australian cohort study measured maternal and cord blood and found a significant association between cord blood 25(OH)D and decreased risk for eczema at 12 months of age. No association was seen with the results of skin prick tests for environmental and food allergies and IgE testing for food allergy.¹⁶²

- **3–8 y**

No data in original study. A RCT in Japan that randomized 344 3-year-old nursery school children to 1200IU vitamin D per day or placebo found a significant decrease in the incidence of Influenza A among supplemented children after 4 months; the effect was greater in children receiving no other vitamin supplementation at baseline. A prospective study that followed 475 Colombian school-age children for 1 year found an association between baseline serum 25(OH)D and risk for gastrointestinal and ear infections.¹⁵⁷ A prospective study that followed 743 children (3 to 15 years of age) in Canadian Hutterite communities for 6 months observed an association between vitamin D deficiency and insufficiency and risk for viral respiratory tract infections.¹⁵⁸ A UK prospective study that followed 860 mother-infant pairs found no association between maternal serum 25(OH)D at 34 weeks gestation and the incidence of asthma, wheeze, or atopy at 6 years of age.¹⁶³ A longitudinal study in the Netherlands (PIAMA) is assessing associations of nutritional indicators with the risk for asthma in a large birth cohort. The most recent data suggest that rates of asthma and severe asthma at 8 years of age are higher among those whose serum 25(OH)D concentrations were in the lowest or middle tertile at 4 years of age.¹⁶⁴

- **9–18 y**

No data in original study. The Avon Longitudinal Study of Parents and Children, a UK study, measured serum 25(OH)D2 and D3 (using HPLC/ tandem mass spectrometry) in some 14,500 children and found an association between lower levels of 25(OH)D2 at a mean age of 9.8 years and higher levels of wheeze, poor lung function, and flexural (antecubital) dermatitis at a mean age of 15.5 years; higher serum concentration of 25(OH)D3 were associated with higher incidence of flexural dermatitis and wheezing but were not associated with lung function. A nested case control study conducted in Norway observed a trend toward an increasing association of type 1 DM in the first 15 years of life and decreased maternal 25(OH)D concentrations. A U.S. prospective cohort study of children at increased risk for developing Type 1 DM based on an Islet Autoimmune genetic marker, found no association of 25(OH)D concentrations at 9 months of age and subsequent risk for progression to DM.

- **19–50 y**

Three RCTs found no effect of supplemental vitamin D on the risk for respiratory infections among adults. The HUNT study analyzed the association of baseline vitamin D (and other nutrient) status in adults with the risk for asthma 11 years later using data from a large-scale longitudinal survey of health in Norway; they found no association of 25(OH)D concentrations with subsequent risk for asthma among women and a small association in men that disappeared after adjustment for confounders. A nested case control study among U.S. Navy and Marine Corps military personnel observed an association of Type 1 diabetes mellitus (DM) with

serum 25(OH)D concentrations at enlistment (310 cases and 310 matched controls) among white soldiers but not among black or Hispanic soldier. The original report identified NHANES III data that include people in this life stage. Analyses using NHANES III data (general adult populations living in the United States) 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. **The German prospective ESTHER study identified for the current report observed a significant inverse association between serum 25(OH)D concentrations and risk for respiratory disease mortality among adults 50 to 74 years of age. The Finnish Kuipio IHD Risk Factor Study observed an increased risk for pneumonia among the adults, 53 to 73 years of age in the lowest tertile of serum 25(OH)D.**
- **≥71 y**
NHANES III data also include people in this life stage
- **Postmenopause**
No data found in the original report. The current report identified a substudy of the WHI CaD trial that assessed participants at 5.1 years and found no effect of supplementation with 400IU vitamin D and 1000mg calcium on women's risk for rheumatoid arthritis
- **Pregnant & lactating women**
Studies identified for the current report are described above for 0–6 months. One cohort study from UK identified in the original report 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 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report)

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 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	<ul style="list-style-type: none">• 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 ⁵⁵ PAHSG UK (50°N) [17311057]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	singleton pregnancy <17 wk 26.3 0	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA nd	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (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	
NEW Studies										
Jones 2012 ¹⁶² Perth, Australia	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy 33.4 (SD 4.5) 51.5%	Eczema stratified by baseline 25(OH)D levels		X			X		Age, race= of mothers
Mai, 2012 ¹⁶⁶ HUNT Study Nord-Trondelag, Norway	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 39.7 (8.5) 43%	Asthma stratified by baseline 25(OH)D quartiles		X	X		X	X	Age= women controls
Pike, 2012 ¹⁶³ UK	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 30.37 (3.81), y 51.74%	Asthma stratified by baseline 25(OH)D levels	X	X	X		X		
Tolppanen, 2013 ¹⁶⁵ UK, Southwest England	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 9.84 (SD 0.02) 52.1	Asthma stratified by baseline 25(OH)D ₂ and 25(OH)D ₃ tertiles							

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (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	
van Oeffelen, 2011 ¹⁶⁴ Netherlands	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd (nd) 51.9%	Asthma stratified by baseline 25(OH)D tertiles		X				X	
NEW Nested case-control studies—Immune Function—Autoimmune Disease										
Munger, 2013 ¹⁶⁸ US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Presumed healthy 20.6 (4.0) 95.1%	Type 1 Diabetes Mellitus stratified by baseline 25(OH)D tertiles							
Salzer 2012 ¹⁷⁰ Risk of Multiple Sclerosis Gestational Risk factors of Multiple Sclerosis (GRoMS) Sweden	<ul style="list-style-type: none"> • Health status • Mean age (Range), y • Male (%) 	nd 26 (16–60) 7.8%	Multiple Sclerosis stratified by baseline 25(OH)D medians							

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (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	
Sorensen, 2012 ¹⁶⁹ Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 9 (SD 3.6) 51%	Type 1 Diabetes stratified by baseline 25(OH)D quartiles		X			X		
NEW Cohort study—Immune Function—Autoimmune Disease										
Simpson, 2011 ¹⁷¹ Diabetes Autoimmunity Study in the Young (DAISY) US Denver, CO	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	At increased risk for Type 1 Diabetes 11.9 (4.4) 49%	Islet Autoimmune stratified by baseline 25(OH)D levels		X					
NEW Cohort study—Immune Function—Infectious Diseases										
Belderbos, 2011 ¹⁵³ Utrecht, Netherland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 0.77 (0.13) 56%	Respiratory Syncytial Virus Bronchiolitis stratified by 25(OH)D tertiles			X				

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure	
Camargo, 2011 ¹⁵⁴ Wellington (41°S latitude) and Christchurch (43°S latitude), New Zealand	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 0.77 (nd) 51%	Infection and Asthma stratified by 25(OH)D tertiles		X		X	X	X	
Sabetta, 2010 ¹⁵⁹ US Greenwich, CT	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Healthy nd (20–88) 43%	Acute Viral Respiratory Tract Infections stratified by 25(OH)D medians	X	X	X				
Shin 2013 ¹⁵⁵ Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) Korea	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	NR Maternal age: 32.2 (SD 3.4) Newborns Range: (0–6) months Mothers: 0% Newborns: 53.1%	Respiratory tract infections, Acute nasopharyngitis, otitis media, and bronchiolitis stratified by 25(OH)D tertiles	X				X	X	

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (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	
Science 2013 ¹⁵⁸ Canada	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 9.3 (SD 3.4) 47.5%	Respiratory tract infections stratified by 25(OH)D medians		X					
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 62 (SD 6.5) 43.8%	Respiratory disease mortality stratified by 25(OH)D tertiles	X	X		X	X	X	
Thornton 2013 ¹⁵⁷ Bogotá School Children Cohort Bogota, Columbia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	~7–12.5% stunted 8.9 (SD 1.6) 48%	Earache/discharge with fever and Cough with fever stratified by 25(OH)D tertiles		X					
Magnus 2013 ¹⁵⁶ Norwegian Mother and Child Cohort Study Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR NR 0%	Asthma stratified by 25(OH)D quartiles	X	X	X	X	X	X	

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (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	
Aregbesola 2013 ¹⁶⁰ Kuopio Ischemic Heart Disease Risk Factor (KIHD) study Kuopio, Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 62.5 (SD 6.5) 50.9%	Pneumonia stratified by 25(OH)D tertiles	X	X	X		X	X	

Table 30b. Vitamin D and immunologic outcomes: Characteristics of autoimmune disease RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure	
Racovan, 2012 ¹⁶⁷ WHI US	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	Post-menopausal 62.34 (SD 6.91) 0%	Rheumatoid Arthritis (RA) stratified by mother's 25(OH)D medians							

Table 30c. Vitamin D and immunologic outcomes: Characteristics of infectious disease continuous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure	
Li-Ng, 2009 ¹⁵⁰ US Long Island, NY	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	nd 58.1 (SD 13.4) 20.3%	Duration of Upper Respiratory Tract stratified by 25(OH)D levels							
Laaksi, 2010 ¹⁵¹ Pori Brigade, Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy Nd (nd) 100%	Days absent from duty stratified by 25(OH)D ₃ levels		X					

Table 30d. Vitamin D and immunologic outcomes: Characteristics of infectious disease dichotomous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Laaksi, 2010 ¹⁵¹ Pori Brigade, Finland	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	Healthy Nd (nd) 100%	Days absent from duty and self-reported cold symptoms stratified by 25(OH)D ₃ levels		X					
Li-Ng, 2009 ¹⁵⁰	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 58.1 (SD 13.4) 20.3%	Upper respiratory tract stratified by 25(OH)D medians							
Manaseki-Holland, 2012 ¹⁴⁹ Kabul, Afghanistan	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd (nd) 52%	Pneumonia stratified by 25(OH)D ₃ medians							Age groups reported but not mean age, only father's ethnicity reported
Murdoch, 2012 ¹⁵² VIDARIS New Zealand	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) • Mean age (SD), y • Male (%) 	nd 48 (10) 25% 10.4 (2.4) 55%	Days of missed work per episode stratified by 25(OH)D ₃ and Placebo medians							
NEW Studies										
Goldring 2013 ¹⁶¹ UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 3 44%	Wheeze ever and lower respiratory tract infection stratified by 25(OH)D medians	X	X				X	Children of mothers enrolled in a 3-arm RCT of vitamin D administration were prospectively followed

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report)

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 HR, OR, RR	95% CI	P for Trend	Study Quality
Melamed 2008 ⁸⁵ 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 ⁵⁵ 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		
NEW Studies—Allergy/Asthma											
Jones 2012 ¹⁶²	Pregnant or lactating women, non- smoking	eczema	NR	25(OH)D ₃	per 10 nmol/L rise in CB 25(OH)D ₃	78	231	OR=0.857	0.739, 0.995	0.042	A
Mai 2012 ¹⁶⁶	Female 19–65 yrs	asthma	11 yrs	25(OH)D	≥75.0	81	328	OR=1.00	Reference		A
					50.0–74.9	125	555	0.8	0.57, 1.13		
					<50.0	170	566	0.94	0.67, 1.32		
					each 25-nmol/L reduction	376	1449	0.97	0.85, 1.12		
	Male 19–65 yrs	asthma	11 yrs	25(OH)D	≥75.0	33	247	1.00	Reference		
					50.0–74.9	77	384	1.5	0.95, 2.38		
					<50.0	98	462	1.47	0.93, 2.32		
					each 25-nmol/L reduction	208	1093	1.14	0.94, 1.37		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (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 HR, OR, RR	95% CI	P for Trend	Study Quality
Pike 2012 ¹⁶³		current doctor- diagnosed asthma	6 yrs	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	87	836	RR=0.98	0.92, 1.04	0.56	B
		current wheeze in last 12 months				117	833	0.99	0.94, 1.05	0.76	
		any wheeze at or before 6 years				504	823	1.00	0.98, 1.02	0.95	
		transient wheeze				367	707	1.00	0.98, 1.02	0.89	
		persistent late wheeze				137	475	0.98	0.94, 1.03	0.49	
		persistent late wheeze with atopy				46	251	0.91	0.84, 0.99	0.04	
		persistent late wheeze without atopy				48	253	1.01	0.94, 1.09	0.73	
Tolppanen 2013 ¹⁶⁵		wheezing	1 yrs	25(OH)D ₂	per doubling of exposure	141	3323	OR=0.83	0.68, 1.00		B
		asthma				464	3323	0.89	0.78, 1.02		
		flexural dermatitis				300	3748	0.83	0.72, 0.94		
		wheezing	1 yrs	25(OH)D ₃	per doubling of exposure	141	3323	1.14	1.03, 1.28		
		asthma				464	3323	1.02	0.93, 1.12		
		flexural dermatitis				300	3748	1.09	1.00, 1.18		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (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 HR, OR, RR	95% CI	P for Trend	Study Quality
van Oeffelen 2011 ¹⁶⁴		bronchial hyperresponsiveness	8 yrs	25(OH)D	Tertile 1: range 23.1– 60.2 nmol/L	80	204	OR=1.00	Reference		A
					Tertile 2: range 60.7– 78.8 nmol/L	88	209	1.16	0.62, 2.18		
					Tertile 3: range 79.0– 303.8 nmol/L	87	194	1.19	0.63, 2.23		
		atopy			Tertile 1: range 23.1– 60.2 nmol/L	93	346	1.00	Reference		
					Tertile 2: range 60.7– 78.8 nmol/L	101	237	2.19	1.17, 4.12		
					Tertile 3: range 79.0– 303.8 nmol/L	93	279	1.23	0.64, 2.39		
		asthma	5–8 yrs	25(OH)D	Tertile 1: range 23.1– 60.2 nmol/L	NR	NR	1.00	Reference		
					Tertile 2: range 60.7– 78.8 nmol/L	NR	NR	0.97	0.57, 1.65		
					Tertile 3: range 79.0– 303.8 nmol/L	NR	NR	0.68	0.39, 1.19		
		severe asthma			Tertile 1: range 23.1– 60.2 nmol/L	NR	NR	1.00	Reference		
					Tertile 2: range 60.7– 78.8 nmol/L	NR	NR	1.06	0.59, 1.90		
					Tertile 3: range 79.0– 303.8 nmol/L	NR	NR	0.61	0.32, 1.15		
NEW Nested case-control studies—Immune Function—Autoimmune Disease											
Munger 2013 ¹⁶⁸	US Navy, MC active duty	Type 1 Diabetes Mellitus	5.4 yrs	25(OH)D	<75nmol/L	45	102	RR =1	Reference		B
					75–<100nmol/L	76	236	0.6	0.38, 0.97		
					≥100nmol/L	65	220	0.56	0.35, 0.90		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (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 HR, OR, RR	95% CI	P for Trend	Study Quality
Salzer 2012 Risk of Multiple Sclerosis ¹⁷⁰ Gestational Risk factors of Multiple Sclerosis (GRoMS) ¹⁷⁰	0–6 mos 19–50 yrs	Multiple Sclerosis	NR	25(OH)D	≥75nmol/l	192	576	OR =0.39	0.16, 0.98	NR	A
					<75nmol/l			1	Reference		
					≥75nmol/l	37	222	1.8	0.53, 5.8		
					<75nmol/l			1	Reference		
Sorensen 2012 ¹⁶⁹	Pregnant	Type 1 Diabetes	NR	25(OH)D	<55nmol/L	39	94	OR= 2.38	1.12, 5.07	0.031	B
					>54 to 59nmol/L	31	88	1.78	0.85, 3.74		
					>69nmol/L to 89nmol/L	22	75	1.35	0.63, 2.89		
					>89nmol/L	17	71	1	Reference		
NEW Cohort study—Immune Function—Autoimmune Disease											
Simpson 2011 ¹⁷¹ Diabetes Autoimmunity Study in the Young (DAISY)	3–8 yrs	Islet Autoimmune (IA)	9 mos	25(OH)D	Inadequate (≤50)	30	128	HR=0.72	0.24,2.71	0.56	A
					Adequate (>50)			1.00	Reference		
		Type 1 Diabetes	NR	25(OH)D	Inadequate (≤50)	55	185	HR=0.44	0.14, 1.45	0.18	A
					Adequate (>50)			1.00	Reference		
NEW Cohort studies—Immune function—Infectious Diseases											
Belderbos 2011 ¹⁵³	0–6 months	Respiratory Syncytial Virus Bronchiolitis	NR	25(OH)D	<50nmol/L	36		RR= 6.2	1.6, 24.9	0.13	A
					50–74nmol/L	48		1.3	NR		
					≥75nmol/l	72		1	Reference		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (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 HR, OR, RR	95% CI	P for Trend	Study Quality
Camargo 2011 ¹⁵⁴	0–6 months	Respiratory Infection	NR	25(OH)D	≥75nmol/L	NR	NR	OR= 1	Reference		B
					25–74nmol/L	NR	NR	1.35	0.88, 2.08		
					<25nmol/L	NR	NR	2.04	1.13, 3.67	0.03	
		Any Infection			≥75nmol/L	NR	NR	OR= 1	Reference		
					25–74nmol/L	NR	NR	1.49	0.92, 2.43		
					<25nmol/L	NR	NR	2.36	1.17, 4.73	0.02	
	15 mos	Wheeze			per 10nmol/L	331	NR	OR=0.98	0.93, 1.02	0.3	
	3 yrs				per 10nmol/L	472	NR	0.96	0.91, 1.00	0.04	
	5 yrs				per 10nmol/L	533	NR	0.95	0.91, 0.99	0.04	
	5 yrs	Incident asthma			per 10nmol/L	181		OR =1.03	0.97, 1.10	0.02	
Sabetta 2010 ¹⁵⁹	19–50 yrs	Acute Viral Respiratory Tract Infections	4 months	25(OH)D	≥95 nmol/L	3	18	OR= 0.24	0.07, 0.87		A
					<95 nmol/L	81	180	1	Reference	0.015	
Shin 2013 ¹⁵⁵ Cohort for Childhood Origin of Asthma and allergic diseases (COCO A)		respiratory tract infections	6 months	25(OH)D	<25.0	74	180	3.41	1.57, 7.42	0.0008	B
					25.0–74.9	89	292	2.14	1.00, 4.58		
					≥=75.0	9	53	1.00	Reference		
		acute nasopharyngitis			<25.0	67	180	4.64	1.88, 11.44	0.0002	
					25.0–74.9	75	292	2.71	1.11, 6.59		
					≥=75.0	6	53	1.00	Reference		
		otitis media			<25.0	10	180	3.06	0.38, 24.46	0.3625	
					25.0–74.9	18	292	3.42	0.45, 26.15		
					≥=75.0	1	53	1.00	Reference		
		bronchiolitis			<25.0	9	180	2.74	0.34, 22.11	0.4819	
					25.0–74.9	19	292	3.62	0.47, 27.63		
					≥=75.0	1	53	1.00	Reference		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (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 HR, OR, RR	95% CI	P for Trend	Study Quality
Science 2013 ¹⁵⁸		respiratory tract infections	156 days	25(OH)D	per 1-unit change in log levels <25 ≥25 <50 ≥50 <75 ≥75	229	743 4 739 152 591 565 178	0.52 0.72 1.00 1.54 1.00 1.35 1.00	0.35, 0.79 0.13, 3.94 Reference 1.07, 2.21 Reference 1.01, 1.82 Reference	0.002 0.7 0.021 0.043	B
Schottker 2013 ⁷⁶ ESTHER		respiratory disease mortality	9.5 yrs	25(OH)D	<30 30–50 ≥50	13 26 16	1439 4188 3927	NR NR 1.00	NR NR reference		B
Thornton 2013 ¹⁵⁷ Bogotá School Children Cohort		earache/discharge with fever cough with fever	140 days	25(OH)D	Deficient: <50 Insufficient: 50–<75 Sufficient: ≥75 Deficient: <50 Insufficient: 50–<75 Sufficient: ≥75	nr nr nr nr nr nr	48 222 205 48 222 205	2.36 0.35 1.00 0.77 0.53 1.00	1.26, 4.44 0.19, 0.65 Reference 0.57, 1.04 0.44, 0.65 Reference		B
Magnus 2013 ¹⁵⁶ Norwegian Mother and Child Cohort Study		asthma	36 mos	25(OH)D	20 nmol/L increase in 25(OH)D <51 51–75 >75	489 114 187 188	1672 316 584 771	0.91 1.00 0.84 0.67	0.81, 1.02 Reference 0.61, 1.17 0.48, 0.95		B
Aregbesola 2013 ¹⁶⁰ Kuopio Ischemic Heart Disease Risk Factor (KIHD) study		pneumonia	9.8 yrs	25(OH)D3	Tertile 1: 8.9–33.8 Tertile 2: 33.9–50.7 Tertile 3: 50.8–112.8	38 22 13	925 426 70	2.4 1.4 1.0	1.2, 4.9 0.7, 2.8 Reference		B

^A Crude OR

Table 31b. Vitamin D and immunologic outcomes: Results of autoimmune disease RCTs (updated from original report)

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 HR, OR, RR	95% CI	P for Trend	Study Quality
Racovan 2012 ¹⁶⁷ WHI	Postmenopause	Rheumatoid Arthritis	5.1 yrs	Vit D	400IU + Ca 1000ng	45	16283	HR 1.15	0.75, 1.75	0.53	A
					Placebo	41	16238	HR 1	Reference		

Table 31c. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (continuous outcomes) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. Analyzed	Final mean	Final SD	Net Diff	Net Diff 95% CI	Study Quality
Li-Ng 2009 ¹⁵⁰	18– 80 years	Duration of Upper Respiratory Tract	12 wks	Vit D 2000IU/day	78	5.4	4.8	+1.0	-1.2, 1.4	B
				Placebo	70	5.3	3.1	Reference		
Laaksi 2010 ¹⁵¹	18– 28 years	Days absent from duty	6 mos	Vit D3 400 IU	80	2.2	3.2	-0.8	-1.9, 0.3	B
				Placebo	84	3.0	4.0	Reference		

Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Laaksi 2010 ¹⁵¹	18–28 years	Self-reported common cold symptoms	6 months	Vit D3	400 IU	45	80	OR 1.17	0.63, 2.16	0.619	B
				Placebo	Placebo	44	84	1	Reference		
		No days absent from duty		Vit D3	400 IU	41	80	1.89	1.01, 3.54	0.045	
				Placebo	Placebo	30	84	1	Reference		
Li-Ng 2009 ¹⁵⁰	18–80 years	Upper Respiratory Tract	12 weeks	Vit D	2000IU/day	28	78	OR 0.79	0.41, 1.54	0.61	B
					Placebo	29	70	1	Reference		
Manaseki- Holland 2012 ¹⁴⁹	infants aged 1–11 months	All Pneumonia First episode	NR	Vit D3	100,000IU	260	1782 person years	IRR =1.065	0.895, 1.268	0.476	A
					Placebo	2445	1782 person years	1	Reference		
		All Pneumonia repeat episode			100,000IU	138	2031 person years	IRR =1.685	1.282, 2.212	<0.0001	
					Placebo	82	2027 person years	1	Reference		
Murdoch 2012 ¹⁵² VIDARIS	18 yrs & older	No of URTs per person	18 months	Vit D3 & Placebo	100,000IU	3.7	161	RR =0.97	0.85,1.11	0.65	A
					Placebo	3.7	161	1	Reference		
		No. of days if missed work per episode*			100,000IU	0.76	161	RR 1.03	0.81, 1.30	0.82	
					Placebo	0.76	161	RR 1	Reference		
		Duration of symptoms			100,000IU	12	161	RR 0.96	0.73, 1.25	0.76	
					Placebo	12	161	RR 1	Reference		

Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Goldring 2013 ¹⁶¹		wheeze ever	3 yrs	Vit D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	11	56	OR 0.56	0.20, 1.57	0.27	A
					control	14	50	OR 1.00	Reference		
		lower respiratory tract infection			either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	14	54	OR 1.00	0.35, 2.91	1	
					control	11	50	OR 1.00	Reference		

*Included in Table 31d (dichotomous outcomes) because differences reported as relative risks.

Vitamin D and Pregnancy-Related Outcomes

This section includes preeclampsia, small-for-gestational age, and preterm birth.

Preeclampsia

Synopsis

For the current report, two RCTs, two prospective studies, and five nested case control studies were identified that assessed the outcome of risk for preeclampsia. The RCTs, whose results were combined and reported in one article, found that supplementation with 2000IU or 4000IU vitamin D per day decreased the risk for preeclampsia. Both prospective studies observed an association between second-trimester serum 25(OH)D concentrations and decreased risk for preeclampsia. Three of the five nested case control studies observed an association between low 25(OH)D concentrations (<50nmol/L) and preeclampsia or severe preeclampsia.

In the original report, 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 32a-c & 33a-c)

In the current report, two RCTs, whose results were combined and reported in one article, found that supplementation with 2000IU or 4000IU vitamin D per day decreased the risk for preeclampsia.

The U.S. NICHD and Thrasher trials randomized 504 women to receive 0, 2000, or 4000IU vitamin D per day in addition to their prenatal vitamins. Supplementation with 4000IU increased serum 25(OH)D concentrations and resulted in a trend toward lower rates of preeclampsia; increasing maternal serum 25(OH)D concentrations were strongly associated with decreased risk for preeclampsia (OR 0.77, 95% CI 0.57, 1.06) (rated B).⁴²

Two prospective cohort studies observed an inverse association between second-trimester serum 25(OH)D concentrations and risk for preeclampsia. One Chinese study that followed 697 women found that low serum 25(OH)D at 12 to 18 weeks gestation and 24 to 26 weeks gestation was associated with a higher risk for preeclampsia ($p < 0.05$) (rated B).¹⁷² A U.S. study that followed a cohort of 1,141 pregnant women in Camden NJ found that serum 25(OH)D less than 50nmol/L at study entry (13.7 \pm 5.7 weeks gestation) was associated with an increased risk for preeclampsia (OR 2.86, 95% CI 1.28, 6.41) (rated B).¹⁷³

Five nested case control studies assessed the association between maternal serum 25(OH)D concentrations during early or mid-gestation and the risk for subsequent preeclampsia. Three of these studies observed an association between maternal 25(OH)D concentrations and subsequent risk for preeclampsia. One Canadian study of 1,301 women (cases and controls) found that the risk for preeclampsia was increased for women with low 25(OH)D concentrations (<50nmol/L vs. \geq 50nmol/L) during the second trimester but not during the first trimester.¹⁷⁴ A U.S. study of 51 women diagnosed with preeclampsia and 204 matched controls (in a cohort of 3,992 women) that divided midgestational 25(OH)D status into tertiles found that low serum 25(OH)D concentrations (<37.5 nmol/L) was associated with severe preeclampsia.¹⁷⁵ A U.S. study aimed at identifying placental growth

factors that, combined with 25(OH)D concentrations, would predict the risk for preeclampsia found that low maternal 25(OH)D concentrations, by itself, had some predictive power regarding the risk for preeclampsia.¹⁷⁶ Two additional nested case control studies, the Canadian EMMA study and a U.S. study found that low first trimester maternal 25(OH)D levels were not associated with risk for preeclampsia.^{177,178}

In the original report, a nested case-control study evaluated the association between 25(OH)D concentration and risk of preeclampsia.¹⁷⁹ 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**

For the current report, one RCT reported that higher dose vitamin D supplementation decreased the risk for preeclampsia. Two prospective cohort studies and three nested case control studies found an association between low 25(OH)D concentrations at mid-gestation and the risk for preeclampsia, and two nested case control studies found no association with first trimester 25(OH)D concentrations and risk for preeclampsia. In the original report, 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

In the current report, we identified two cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one cohort study and one nested case control study that assessed the association with preterm birth. One of the two cohort studies found an increase in the risk for SGA at the lowest concentration range of maternal serum 25(OH)D

compared with higher serum vitamin D concentrations among both white and black women; the other study observed a U-shaped association between serum 25(OH)D and the risk for risk for SGA among white women. The prospective study observed an increase in the risk for preterm birth among women carrying twins whose serum 25(OH)D was less than 75nmol/L. The nested case control study that assessed the association with preterm birth found no significant association.

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

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

Detailed Presentation (Tables 32a-c & 33a-c)

In the current report, two cohort studies assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a SGA infant and one nested case control study that assessed the association with preterm birth.

One U.S. cohort study of 1,067 white and 236 black mother-infant pairs found an association of serum 25(OH)D less than 25nmol/L with an increased risk for SGA, compared with serum 25(OH)D of 25nmol/L or greater (adjusted OR 3.94 [1.51, 10.29]). When the data were further adjusted for race, the adjusted odds ratio fell slightly (3.17 [1.16, 8.63]).⁴⁵

The other cohort study, which assessed 412 mother-infant pairs, found a U-shaped association between serum 25(OH)D and risk for SGA among white mothers. The lowest risk was observed from 60 to 80 nmol/L; compared with serum 25(OH)D 37.5–75 nmol/L, SGA odds ratios (95% CI) for levels, 37.5 and 75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8), respectively. This association was not seen among black mothers (study rated A).¹⁸⁰

A multisite U.S. prospective study of 211 twin pregnancies found that late second trimester serum 25(OH)D concentrations of 75nmol/L or greater were associated with a decreased risk for preterm birth (aOR 0.40, 95%CI 0.2, 0.8) (rated A).¹⁸¹ One Canadian nested case control study of 227 mother infant pairs, the EMMA study, found no association of low maternal serum 25(OH)D (<37.5nmol/L) at 10 to 21 weeks gestation with the risk for preterm birth.¹⁷⁷

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**
In the current report, we identified two cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one nested case control study that assessed the association with preterm birth. The two cohort studies found an increase in the risk for SGA at the lowest concentration range of maternal serum 25(OH)D compared with higher serum vitamin D concentrations. One study found this increase in risk for both white and black mothers, whereas the other study found that the risk increased only for white mothers. A prospective study observed an increase in the risk for preterm birth among women carrying twins whose serum 25(OH)D was less than 75nmol/L at mid-gestation. A nested case control study that assessed the association of serum 25(OH)D with preterm birth found no significant association. We found no studies for the current report on the relationship of maternal serum 25(OH)D and pregnancy hypertension.

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report)

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 ¹⁷⁹ PEPPS ^A US (41°N) [17535985]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Healthy 20–29 0%	<ul style="list-style-type: none">• Assay method• Season blood drawn	ELISA ND	Comparison of mean 25(OH)D levels in cases and controls		x	x			
NEW Studies											
Wei, 2012 ¹⁷⁴ International Trial of Antioxidants in the Prevention of Preeclampsia (INTAPP) Canada	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of preeclampsia 30.3 (4.8) 0%			Preeclampsia stratified by 25(OH)D tertiles		X	X	X	X	X
Shand, 2010 ¹⁷⁷ EMMA Vancouver, Canada	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd nd 0%			Preeclampsia stratified by 25(OH)D medians	X	X	X		X	X
Baker, 2010 ¹⁷⁵ US Chapel Hill, NC	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Healthy 28 (23–34) 0%			Severe preeclampsia stratified by 25(OH)D tertiles		X	X		X	
Powe, 2010 ¹⁷⁸ US Boston, MA	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 30.4 (SD 6) 0%			Severe preeclampsia stratified by 25(OH)D quartiles		X			X	

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Woodham 2011 ¹⁷⁶ Chapel Hill, UK	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd 29 (25–33) 0%	Severe preeclampsia stratified by 25(OH)D		X	X		X	
Scholl 2013 ¹⁷³ Camden Study Camden, New Jersey US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy/NR 22.8 (SD 5.4) 0%	Preeclampsia stratified by 25(OH)D quartiles	X	X	X			X
Wei 2013 ¹⁷² INTAPP Canada	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 28.68 (SD 5.44) 0%	Preeclampsia stratified by 25(OH)D medians		X	X		X	X

^APregnancy Exposures and Preeclampsia Prevention Study

Table 32b. Vitamin D and other pregnancy outcomes: Characteristics of observational studies (updated from original report)

Table 2. Main Results and Other Pregnancy Outcomes: Characteristics of Observational Studies (adapted from original reports)				Confounders/Effect Modifiers Adjusted						
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
NEW Studies										
Baker 2011 ¹⁸²	Health status Mean age (Range), y Male (%)	Healthy 33 (30–37) 0		Preterm birth 25(OH)D tertiles		X	X		X	
Bodnar, 2010 ¹⁸⁰ US Pittsburgh, PA (latitude 40 degree N)	• Health status • Mean age (Range), y • Male (%)	Healthy 21 (14–35) 0%		Small-for-gestational age births stratified by 25(OH)D tertiles		X	X			X
Burris 2012 ⁴⁵ US, Massachusetts	• Health status • Mean age (SD), y • Male (%)	nd 33 (SD 4.5) 0%		Small-for-gestational age births stratified by 25(OH)D tertiles		X	X		X	
2013 ¹⁸¹ US	• Health status • Mean age (SD), y • Male (%)	nd NR 0%		Preterm birth at less than 35 wk and Preterm birth at less than 32 wk stratified by 25(OH)D sextiles		X	X		X	X

Table 32c. Vitamin D and preeclampsia: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
NEW Studies										
Wagner 2013 ⁴² US	<ul style="list-style-type: none">• Health status• Mean age (Range), y• Male (%)	nd 27 (18–41) 0%		Preeclampsia stratified by 25(OH)D tertiles		X				

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report)

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 ^{179A} 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	1.7, 14.1	B
NEW Studies										
Wei 2012 ¹⁷⁴		preeclampsia	12–18 weeks gestation	25(OH)D	per SD increase	32	697	0.79	0.52, 1.20	A
					<50	15	272	1.24	0.58, 2.67	
					>50	17	425	1.00	Reference	
			24–26 weeks gestation		per SD increase	28	604	0.68	0.44, 1.05	
					<50	19	236	3.24	1.37, 7.69	
					>50	9	368	1.00	Reference	
			Shand 2010 ¹⁷⁷			preeclampsia	10–20 weeks gestation	25(OH)D	<37.5	
≥37.5	18	NR		1.00					Reference	
<50	17	NR		1.39					0.54, 3.53	
≥50	11	NR		1.00					Reference	
<75	21	NR		0.57					0.19, 1.66	
≥75	6	NR		1.00					Reference	
Baker 2010 ¹⁷⁵	Pregnant or lactating women	severe preeclampsia		NR					25(OH)D	< 50
			50–74.9		10	51	2.16	0.85, 5.40		
			≥75		11	30	1.00	Reference		

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report) (continued)

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
Powe 2010 ¹⁷⁸		severe preeclampsia	NR	25(OH)D	Quartile 1 (ND)	39 (overall)	170 (overall)	1.50	0.57, 3.96	B
					Quartile 2 (ND)			1.04	0.39, 2.76	
					Quartile 3 (ND)			0.67	0.23, 1.91	
					Quartile 4 (ND)			1.00	Reference	
Scholl 2013 ¹⁷³ Camden Study		preeclampsia	20 weeks gestation	25(OH)D	<30	12	121	2.13	1.07, 4.26	
					30–40	12	116	2.09	1.04, 4.22	B
					40–50	7	154	0.94	0.41, 2.17	
					>=50	38	750	1.00	Reference	
Wei 2013 ¹⁷² INTAPP		preeclampsia	24–26 weeks gestation	25(OH)D	<50 nmol/L	NR	NR	2.97	1.23, 7.20	B
					>=50 nmol/L			1.00	Reference	
Woodham 2011 ¹⁷⁶		severe preeclampsia	NR	25(OH)D		41	164	0.95	0.94, 0.97	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.

Table 33b. Vitamin D and other pregnancy outcomes: Results of observational studies (updated from original report)

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
Baker 2011 ¹⁸²		preterm birth	NR	25(OH)D	<50 nmol/L	3	11	0.82	0.19, 3.57	A
					50–74.9 nmol/L	8	32	0.87	0.34, 2.25	
					≥75 nmol/L	29	117	1.00	Reference	
Bodnar 2010 ¹⁸⁰	Pregnant or lactating women	Small-for- gestational age births	NR	25(OH)D	<37.5 nmol/L	8	11	7.5	1.8, 31.9	A
white women					37.5–75 nmol/L	27	134	1.0	Reference	
					>75 nmol/L	42	128	2.1	1.2, 3.8	
	black women	Small-for- gestational age births	NR	25(OH)D	<37.5 nmol/L	17	65	1.5	0.6, 3.5	
					37.5–75 nmol/L	13	63	1.0	Reference	
					>75 nmol/L	4	11	2.2	0.5, 9.0	
Bodnar 2013 ¹⁸¹		preterm birth at less than 35 wk	24–28 weeks gestation	25(OH)D	< 75	42	85	1.0	Reference	A
	≥75				33	126	0.4	0.2, 0.8		
	per 1-SD increase				75	211	0.5	0.3, 0.8		
	Q1 (median 43.6)				27	52	1.0	Reference		
	Q2 (median 72.7)				24	53	1.0	0.4, 2.5		
	Q3 (median 95.4)				15	53	0.4	0.2, 1.1		
	Q4 (median 116)				9	53	0.2	0.1, 0.7		
	< 75				16	85	1.0	Reference		
	≥75	9	126	0.2	0.1, 0.6					
	per 1-SD increase	25	211	0.4	0.2, 0.8					
	Q1 (median 43.6)	10	52	1.0	Reference					
	Q2 (median 72.7)	7	53	0.5	0.1, 1.7					
	Q3 (median 95.4)	6	53	0.4	0.1, 1.5					
	Q4 (median 116)	2	53	0.1	0.02, 0.7					

Table 33c. Vitamin D and preeclampsia: results of RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Wagner 2013 ⁴²		Preeclampsia	NR	2000 IU	9	201	RR 0.55	0.22, 1.34	0.43	B
				4000 IU	4	193	RR 0.25	0.08, 0.80	0.05	
				control	9	110	RR 1.00	Reference		

Vitamin D and Clinical Outcomes of Bone Health

The current report sought RCTs and observational studies reporting on the association between vitamin D intervention or exposure and clinical outcomes related to bone health, including rickets, fractures, muscle strength, and falls, published since the original report.

For bone health outcomes, **the original report** (e.g., bone mineral density, fracture, fall or muscle strength) 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).⁸ 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

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

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 (not updated from original report)

From original report			
Author Year [PMID]	Cranney 2007 ⁸ [18088161]		
Design	Systematic review of RCTs and observational studies		
Population	<ul style="list-style-type: none">• 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): <ul style="list-style-type: none">• Include vitamin D₂ or D₃ with or without calcium.• Exclude vitamin D preparations, calcitriol, α-calcidol (because they are not nutritional supplements, and have different safety profile) Comparator: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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

The current report did not identify any new trials that assessed the effect of interventions of vitamin D alone on fracture risk; eight observational studies assessed the association between serum 25(OH)D and fracture risk; (interventions that assessed the effect of vitamin D and calcium are described in Table 59 and the accompanying text). We identified two RCTs that examined the effect of supplementation with vitamin D on the risk for falls, and two RCTs on muscle strength; four prospective cohort studies assessed the association between serum(OH)D concentrations and muscle strength, and one prospective cohort study assessed the association between serum 2(OH)D and falls. The RCTs reported significant effects of vitamin D supplementation on decreasing risk for falls and increasing muscle strength. Three of the four prospective cohort studies reported associations between lower serum 25(OH)D and decreased or decreasing muscle strength and performance; the fourth saw no association. An association was seen between lower 25(OH)D concentrations and increased risk for falls. The studies are described in detail below.

Overall, the Ottawa EPC report, summarized in the original 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.⁸

Findings from three additional RCTs (published after the Ottawa EPC report)¹⁸³⁻¹⁸⁵ also did not show significant effects of either vitamin D₂ or D₃ 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 35a-d & 36a-d)

RCTs of Vitamin D Supplementation Identified for the Current Report that Assessed the Effects on Falls and Muscle Strength

Two RCTs were identified for the current report that examined the effects of vitamin D supplementation on the risk for falls among older adults (both rated A). A 1-year study of 242 adults in Germany, 70 to 91 years of age (average age 77, 75% women) randomized the group to receive 800IU vitamin D and 1000mg calcium daily or calcium and placebo alone; the vitamin D group had a significant decrease in the number of first fallers (OR 0.73 [0.54, 0.96]).¹⁸⁶ A 1-year study of 382 postmenopausal Australian women, 70 to 90 years of age randomized the women to receive 1000IU vitamin D₂ and 1000mg calcium daily or placebos; supplemented women had a significantly decreased risk of falling especially in winter and a decreased risk for first falls but not for two or more falls.¹⁸⁷

Two RCTs were identified for the current report that examined the effects of 1 year of vitamin D supplementation on muscle strength (both rated A). The two studies assessed the effect of supplementation with vitamin D and calcium (compared with calcium alone) on strength in older adults. A 1-year study of 242 adults in Germany, 70 to 91 years of age (average age 77, 75% women) randomized the group to receive 800IU vitamin D and 1000mg calcium daily or calcium and placebo alone; the vitamin D group had significant improvements in muscle strength and in timed up and go.¹⁸⁶ A study of 261 community dwelling, vitamin D insufficient, Australian women, 70 to 90 years of age, were randomized to 1,000IU vitamin D and 1000 mg calcium daily or calcium alone: only women with the lowest baseline muscle strength had significant improvements.¹⁸⁸

Observational Studies of Muscle Strength and Risk for Falls

Four prospective cohort studies were identified for the current report that assessed the association between serum 25(OH)D concentrations and muscle strength or loss among older adults. Among a subset of the WHI cohort serum 25(OH)D concentrations of 75nmol/L or more were associated with higher muscle strength and performance scores at 6 years' followup (study rated A).¹⁸⁹ The Rancho Bernardo Study, which followed a cohort of 1,065 men and women of average age 74.6 over 2.5 years found that lower serum 25(OH)D concentrations were associated with declining muscle function in women but not in men (rated C).¹⁹⁰ A study of 646 men and women in Tasmania, average age 62, over 2.6 years, found that serum 25(OH)D concentrations of 50nmol/L or less were associated lower muscle strength at followup (rated B).¹⁹¹ The Health ABC Study followed 2,641 men and women, ages 70 to 80, over 4 years and found that lower serum 25(OH)D concentrations were not associated with a faster rate of decline in muscle strength over time (rated B).¹⁹²

The one cohort study that assessed the association between serum 25(OH)D and risk for falls followed 463 men and women, 70 to 90 years of age over 1 year and found that serum 25(OH)D of 50nmol/L or less was associated with an increased risk for falls (rated B).¹⁹³

Observational Studies of Fracture Prevention Identified for the Current Report

Eight prospective cohort and nested case control studies that assessed the association between vitamin D exposure and fracture risk were identified that met the inclusion criteria for the current study.

Hip fracture risk was assessed in five studies that ranged in followup from a median of 6.4 years to an average of 11 years. The Cardiovascular Health Study, a prospective cohort study that followed 1,621 older community dwelling adults over 11 years and found a small but significant increase in hip fracture risk for those with the lowest serum levels of 25(OH)D (rated A).⁸⁷ The Health ABC study, which followed a population of 2,501 older adults for a median of 6.4 years, found no significant association of 25(OH)D exposure and risk for hip fracture (rated B).¹⁹⁴ A reassessment of a subgroup of women in the WHI Observational Study (OS) found an association of low vitamin D and increased risk for hip fracture (rated B).¹⁹⁵ A study that assessed the risk for hip and other osteoporotic fracture among 4,749 NHANES III participants ages 65 and over found that among those followed for less than 10 years, serum 25(OH)D was a significant predictor for hip and other major osteoporotic fracture; however at 10 years or more, the association was no longer significant (rated A).¹⁹⁶ The NOREPOS study followed a cohort of 21,774 men and women 65 to 79 years of age for 10.7 years and observed that low serum 25(OH)D (less than 42.2 nmol/L) predicted a 38 percent increased risk for hip fracture in this population (95% CI 9, 74) compared with a 25(OH)D concentration of 67.9 nmol/L or more (rated A).¹⁹⁷ Nonvertebral fracture risk was assessed in two studies (both with B ratings). One nested case control study of the MrOS study population of older men found no association between low serum 25(OH)D alone and nonvertebral fracture risk.¹⁹⁸ The Health ABC cohort study found no significant association of serum 25(OH)D with nonvertebral fracture risk.¹⁹⁴

Total fragility fracture was assessed in two studies. A reassessment of WHI OS data after 8.6 years follow up found an association of lower serum 25(OH)D concentrations with a significantly increased fracture risk for white women but a much smaller association for black women, no association for Hispanic or native American women, and an association of higher 25(OH)D concentrations with higher risk for fragility fracture in Asian American women (results of the WHI CaD trial are discussed later in the section on vitamin D and calcium supplementation).¹⁹⁹ The CEOR study, a study of postmenopausal Saudi women with a follow up of 5.2 years, observed that low vitamin D was an independent predictor of increased risk for osteoporotic fracture.²⁰⁰

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)¹⁸³⁻¹⁸⁵ that examined the effect of either vitamin D₂ or D₃ 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^{183,184} 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.¹⁸⁵ 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.¹⁸³⁻¹⁸⁵ 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.¹⁸³

Findings by Life Stage

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

A single RCT identified for the current report reported no significant effect of

vitamin D supplementation of 12 to 14-year old girls on muscle strength, in spite of improved serum status. Not reviewed in the original report

- **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**
Two of three trials identified for the current report that assessed the effects of vitamin D₂ or D₃ supplementation on the risk for falling among men and women 70 and older reported a significant decrease in the risk for some categories of falls. Two trials identified for the current report that assessed the effects of vitamin D₂ or D₃ supplementation on muscle strength reported some improvement but this finding was limited to those with lowest baseline strength in one study. Analysis of elderly adults in two large prospective cohort studies found a strong inverse association between serum 25(OH)D and risk for hip fracture and major osteoporotic fracture; however one of the studies observed the association only at followup times of 10 years or less. In the original report, findings from three new RCTs did not show significant effects of either vitamin D₂ or D₃ 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**
Of two trials identified for the current report that assessed the effects of vitamin D₂ or D₃ supplementation on the risk for falling among postmenopausal women 70 and older, one reported a significant decrease in the risk for some categories of falls, and one reported no effect. This trial reported improved muscle strength among postmenopausal women 70 and older but only in those with lowest baseline strength. 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 **identified for the original report.**
- **Pregnant & lactating women**
Not reviewed

Table 35a. Vitamin D and bone health: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lyons 2007 ¹⁸⁵ South Wales, UK (52°N) [17473911]	<ul style="list-style-type: none"> • 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 ¹⁸⁴ Scotland (55° 57'N) [17656420]	<ul style="list-style-type: none"> • 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 ¹⁸³ Chile (32°S) [16797903]	<ul style="list-style-type: none"> • 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)	
NEW Studies						
Pfeifer, 2009 ¹⁸⁶ Bad Pyrmont, Germany Graz, Austria	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 77 (SD 4) 26%	25(OH)D: 22.0 nmol/L	1000mg and 800 IU daily vs. 1000mg daily	>80% (noncompliant participants excluded)	
Prince, 2008 ¹⁸⁷ Perth, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Vitamin d deficient/depleted 77.4 (5) Range: 0–90 0%	25(OH)D: ≤40 nmol/L	1000mg of Ca & 1000 IU of Vit D ₂ daily vs. 1000mg of Ca & placebo daily	92% (tablet counting)	

Table 35b. Vitamin D and muscle strength: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Lips, 2010 ²⁰¹ Multiple countries; North America(9 centers); Europe (3 centers)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 77.6 (SD 6.6) nd	serum vitamin D- placebo- 35.3+/-13.8 nmol/l, D3- 34.25+/-11.0 nmol/l serum calcium- placebo- 9.4+/- 0.4mg/dl, D3- 9.4+/- 0.4mg/dl	Double placebo vs. 60,000 IU/week Vs. 500mg/twice daily & 60,000 IU/week	All completes were adherent	
Pfeifer, 2009 ¹⁸⁶ Bad Pyrmont, Germany Graz, Austria	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 77 (SD 4) 26%	Serum vitamin D level:55±18 nmol/L Calcium intake: 608±38 mg/d	1000 mg & 800 IU daily Vs. 1000 mg daily	>80% (noncompliant participants excluded)	
Ward, 2010 ²⁰² Manchester, UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 13.8 (SD 0.7) Range: 12–14 11.6	total serum 25OHD placebo: 17.9 ± 7.4 nmol/l vit D group: 18.1 ± 8.0 nmol/l	150,000 IU/ quarterly Vs. Placebo	100%	
Zhu, 2010 ¹⁸⁸ Perth, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	plasma 25(OH)D concentration less than 60 nmol/L 77 (SD 4.8) 0%	Serum 25(OH)D 17.7 ±10.5 nmol/L	1,000 mg/d Ca +1,00 IU vit D2 Vs. 1,000 mg/d Ca	vitamin D group: 86.7% control group: 86.8%	

Table 35c. Vitamin D and muscle strength: Characteristics of prospective cohorts (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Dam, 2009 ¹⁹⁰ Rancho Bernardo study California, US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 74.6 (SD 10.3) 38%	serum vitamin D: men- 107.6±29.2 nmol/L, women- 100.8±33.1 nmol/L	10–80 nmol/l 82.5–97.5 nmol/l 100–112.5 nmol/l 115–337.5 nmol/l Vs. 10–90 nmol/l 92.5–102.5 nmol/l 105–120 nmol/l 122.5–262.5 nmol/l	nd	
Houston, 2012 ¹⁹² Healthy, Aging and Body Composition US Pittsburgh, Memphis	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	diabetes, cvd, copd, knee pain 74.7 (SD 2.9) 49%	1/3– 25(OH)D <50nmol/L, 2/3– <75nmol/L	<50 nmol/L Vs. 50–<75 nmol/L Vs. ≥75 nmol/L	nd	
Menant, 2012 ¹⁹³ Sydney, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 78 (SD 4.6) Range: 70–90 46%	Serum vitamin D– 62.2±24.6 nmol/L	≤ 50nmol/l Vs. > 50nmol/l	nd	
Scott, 2010 ¹⁹¹ Tasmanian Older Adult Cohort Study (TASOAC) Tasmania, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	plasma 25(OH)D concentration less than 60 nmol/L 62 (SD 7) Range: 50–79 51%	Serum 25OH(D) Low vitamin D: 37.1±8.4 High vitamin D: 67.8±13.4	> 50nmol/l Vs. ≤ 50nmol/l	nd	

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 74.6 (SD 4.6) 30%	Serum vitamin D: 66.2+/-25.8 nmol/L	Normal level Vs. Low level (season specific, ranges 43–61 nmol/L)	nd	
Barbour, 2012 ¹⁹⁴ US Pittsburgh, PA and Memphis, TN	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd nd	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532– 995) 719 (517–978) 716 (501– 940) Supplemental calcium intake (%) yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (%) yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes, any non-spine fracture no/yes	Quartile 1: ≤44.5 nmol/l vs. Quartile 2: 44.5–60.9 nmol/L vs. Quartile 3: 60.9–79.9 nmol/L vs. Quartile 4: >79.9 nmol/L	nd	
Barrett-Connor, 2012 ¹⁹⁸ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, Overweight/Obese, and diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12% 74 (SD 6) 100%	nd	Normal level Vs. Low vit D	nd	

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Burgi 2011 ²⁰³ US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 19.5 (SD 1.8) 0%	nd	3.8–49.3 nmol/L vs. 49.3–66.5 nmol/L vs. 66.5–82.0 nmol/L vs. 82.0–99.5 nmol/L vs. 99.5–281.3 nmol/L	Nd
Cauley 2011 ¹⁹⁹ WHI OS US	<ul style="list-style-type: none"> • Health status • Mean age (Range), y • Male (%) 	nd 64 (50–70) nd	nd	<50 nmol/L vs. 50–<75 nmol/L vs. ≥75 nmol/L	nd
Michael, 2011 ¹⁸⁹ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 70.3 (SD 3.7) Range: 50–79 0%	Serum vitamin D- 48.2±21.4 nmol/L	≥ 75 nmol/l Vs. 50–74nmol/l Vs. 25–49 nmol/l Vs. ≤ 25 nmol/l	nd
Rouzi 2012 ²⁰⁰ Jeddah, Saudi Arabia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 61.3 (SD 7.2) nd	Serum 25(OH)D: 34.27±22.80 nmol/L	<17.90 nmol/L vs. >45.1 nmol/L	nd
Cauley, 2008 ¹⁹⁵ WHI-OS nd	<ul style="list-style-type: none"> • Health status • Mean age (Range), y • Male (%) 	Post-menopausal Nd (50–79) 0%	Serum 25(OH)D controls: 59.60 ± 18.05 nmol/l cases: 55.95 ± 20.28 nmol/l	Quartile 1: 9.2–47.5 nmol/L vs. Quartile 2: 47.6– 70.6 nmol/L vs. Quartile 3: 60.2– 70.6 nmol/L vs. Quartile 4: 70.7– 121.5 nmol/L vs. per 2.5 nmol/L decrease vs. per 25 nmol/L decrease	nd
Looker 2013 ¹⁹⁶ NHANES III US (multiple cities)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 75.2 25.7%	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L	3 categories per 1 SD unit decline in serum 25OHD	nd

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Menant, 2012 ¹⁹³ Sydney, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 78 (SD 4.6) Range: 70–90 46%	serum vitamin D- 62.2±24.6 nmol/L	≤ 50nmol/l Vs. > 50nmol/l	nd
Michael, 2011 ¹⁸⁹ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 70.3 (SD 3.7) Range: 50–79 0%	Serum vitamin D- 48.2+/-21.4 nmol/L	≥ 75 nmol/l Vs. 50–74nmol/l Vs. 25–49 nmol/l Vs. ≤ 25 nmol/l	nd
Holvik 2013 ¹⁹⁷ Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	46.1–59.2% good or very good health 71.9 (SD 3.9) 28%	median (25th and 75th percentiles) s- 25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L	Quartile 1: 4.5–42.1 vs. Quartile 2: 42.2– 53.5 vs. Quartile 3: 53.5– 67.8 vs. Quartile 4: 67.9– 250.0	nd

Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original 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 ¹⁸⁵ [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 ¹⁸⁴ [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 ¹⁸³ [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					

Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

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
NEW Studies												
Pfeifer, 2009 ¹⁸⁶ Multiple Countries		Primary–Falls (≥1)	1°	12 mo	1000 mg & 800 IU daily	NR	122	RR	0.73	0.54, 0.96	<0.01	A
					1000 mg daily	NR	120	RR	1.00	Reference		
Prince, 2008 ¹⁸⁷ Perth, Australia	Primary–Falls (≥1)	1°	1 y		1000mg of Ca & 1000 IU of Vit D2 daily	80	151	OR	0.66	0.41, 1.06	NS	A
					1000mg of Ca & placebo daily	95	151	OR	0.61	0.37, 0.99 adjusted for height	< 0.05	
					1000mg of Ca & placebo daily	95	151	OR	1.00	Reference		
	Primary–1 fall				1000mg of Ca & 1000 IU of Vit D2 daily	32	151	OR	0.50	0.28, 0.88	< 0.05	
					1000mg of Ca & placebo daily	51	151	OR	1.00	Reference		
	Primary–Falls (≥2)				1000mg of Ca & 1000 IU of Vit D2 daily	NR	151	OR	0.86	0.50, 1.49	> 0.05	
					1000mg of Ca & placebo daily	NR	151	OR	1.00	Reference		
	Primary–First fall in winter/spring				1000mg of Ca & 1000 IU of Vit D2 daily	38	151	OR	0.55	0.32, 0.96	< 0.05	
					1000mg of Ca & placebo daily	54	151	OR	1.00	Reference		
	Primary–First fall in summer/autumn				1000mg of Ca & 1000 IU of Vit D2 daily	42	151	OR	0.81	0.46, 1.42	> 0.05	
					1000mg of Ca & placebo daily	41	151	OR	1.00	Reference		

Note: Outcomes cells are shaded for the Control rows.

^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

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions , Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Lips, 2010 ²⁰¹ Multiple countries; North America(9 centers); Europe (3 centers)	71+	Short physical performanc e battery (SPPB) summary score	2°	16 wk	8,400 IU/weekly	109		9.00	change= 0.355	0.108, 0.601	-0.25	-0.60, -0.10	0.17	A
					Placebo	104		9.07	change= 0.601	0.351, 0.852	Reference	NR		
		Short physical performanc e battery (SPPB) gait speed			8,400 IU/weekly	109	cm/s	93.70	change= 3.10	-0.252, 6.458	-0.84	-5.63, 3.95	0.73	
					Placebo	104	cm/s	88.70	change= 3.94	0.567, 7.38	Reference	NR		
Pfeifer, 2009 ¹⁸⁶	71+	Secondary- Quadriceps strength left leg	2°	12 mo	1000 mg & 800 IU daily	114	Newto n	211.00	final= 236	SD=75	+12	-8.6, 32.6	0.25	A
Bad					1000 mg daily	114	Newto n	217.00	final= 224	SD=83	Reference			
Pyrmont, Germany Graz, Austria		Secondary- Body sway total length			1000 mg & 800 IU daily	114	mm	86.00	final= 81	SD=32	-5	-13, 3	0.22	
					1000 mg daily	114	mm	90.00	final= 86	SD=30	Reference			
		Secondary- Timed up and go (TUG)			1000 mg & 800 IU daily	114	secs	9.00	final= 7.5	SD=3.4	-0.8	-1.9, 0.3	0.16	
					1000 mg daily	114	secs	8.50	final= 8.3	SD=5.1	Reference			

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Intervention s, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality	
Ward, 2010 ²⁰² Manchester, UK	9–18 yrs	Maximum force	1°	1 yr	150,000 IU/ quarterly	33	kN/kg	2.80	change= -0.08	SD=0.22	-0.04	-0.12, 0.04	0.32	A	
					Placebo	32	kN/kg	2.71	change= -0.04	SD=0.04	Reference				
		Eslinger fitness index			150,000 IU/ quarterly	33	Per- cent	89.44	change= -4.31	SD=9.32	+0.17	-3.8, 4.2	0.93		
					Placebo	32	perce nt	85.41	change= -4.48	SD=6.68	Reference				
		Efficiency			150,000 IU/ quarterly	33	Per- cent	87.76	change= 2.72	SD=8.57	+1.10	-0.91, 3.12	0.10		
					Placebo	32	Per- cent	84.36	change= -0.56	SD=7.42	Reference				
		Velocity			150,000 IU/ quarterly	33	m/sec	2.19	change= 0.02	SD=0.13	+0.03	-0.03, 0.09	0.28		
					Placebo	32	m/sec	2.12	change= -0.01	SD=0.09	Reference				
		Jump height			150,000 IU/ quarterly	33	m	0.34	change= 0.01	SD=0.04	+0.01	-0.01, 0.03	0.32		
					Placebo	32	m	0.33	change= 0.00	SD=0.04	Reference				
		Maximum power relative to body weight			150,000 IU/ quarterly	33	kW/kg	39.52	change= -1.06	SD=4.18	+0.18	-1.6, 2.0	0.84		
					Placebo	32	kW/kg	37.81	change= -1.24	SD=2.91	Reference				
		Spine bone mineral content (BMC)			150,000 IU/ quarterly	35	g	11.73	change= 0.52	SD=0.39	-0.05	-0.24, 0.15	0.62		
					Placebo	33	g	11.97	change= 0.57	SD=0.43	Reference				
		Tibia 66% cortical bone mineral content (Ct BMC)			150,000 IU/ quarterly	33	mg/ mm	268.38	change= 7.68	SD=12.26	-1.98	-8.4, 4.4	0.54		
					Placebo	31	mg/ mm	261.23	change= 9.66	SD=13.38	Reference				

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Intervention s, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality	
Zhu, 2010 ¹⁸⁸ Perth, Australia	71+	Timed up and go (TUAG)	1°	1y	1,000 mg/d Ca +1,00 IU vit D2	129	secs	11.0	Final=8.1	SD=3.9	-0.9	-2.2, 0.5	0.2	A	
					1,000 mg/d Ca	132	secs	10.8	Final=9	SD=7	Reference				
		lower limb muscle strength: ankle dorsiflexion			1,000 mg/d Ca +1,00 IU vit D2	129	kg	11.6	Final=10.9	SD=3.7	0	-0.9, 0.9	1		
		1,000 mg/d Ca			132	kg	11.8	Final=10.9	SD=4	Reference					
		lower limb muscle strength: knee flexor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	11.8	Final=12.9	SD=3.5	-0.1	-1.0, 0.8	0.83		
		1,000 mg/d Ca			132	kg	11.9	Final=13	SD=3.9	Reference					
		lower limb muscle strength: knee extensor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	18.3	Final=18	SD=5	-0.3	-1.6, 1.0	0.65		
		1,000 mg/d Ca			132	kg	18.8	Final=18.3	SD=5.5	Reference					
		lower limb muscle strength: hip extensor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.6	Final=17.2	SD=5.2	+0.3	-1.1, 1.7	0.67		
		1,000 mg/d Ca			132	kg	14.4	Final=16.9	SD=6.2	Reference					
		lower limb muscle strength: hip abductor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	12.3	Final=14.5	SD=4.1	+0.4	-0.7, 1.5	0.48		
		1,000 mg/d Ca			132	kg	12.2	Final=14.1	SD=4.9	Reference					
		lower limb muscle strength: hip flexor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.5	Final=15.4	SD=4.2	0	-1.1, 1.1	1		
		1,000 mg/d Ca			132	kg	14.5	Final=15.4	SD=4.8	Reference					
		lower limb muscle strength: hip adductor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.4	Final=16.4	SD=4.2	+0.1	-1.1, 1.3	0.86		
		1,000 mg/d Ca			132	kg	14.7	Final=16.3	SD=5.2	Reference					

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Dam, 2009 ¹⁹⁰ Rancho Bernardo study California, US		Change in grip strength (women)	2°	2.5 y (median)	10–80 nmol/l	159	kg (%)	NR	Change=	-4.76,	+1.55	NC	0.22	C
					82.5–97.5 nmol/l	181			Change=	-1.34,				
					100–112.5 nmol/l	153			Change=	-6.85,				
					115–337.5 nmol/l	163			Change=	-7.10,				
		Change in grip strength (men)			10–90 nmol/l	114			Change=	-2.12,	+1.63	NC	0.22	
					92.5–102.5 nmol/l	86			Change=	-3.91,				
					105–120 nmol/l	110			Change=	-2.34,				
					122.5–262.5 nmol/l	99			Change=	-5.15,				
		Change in Timed up and go (TUG)(women)			10–80 nmol/l	159			Change=	16.22,	+13.79	NC	0.002	
					82.5–97.5 nmol/l	181			Change=	2.69,				
					100–112.5 nmol/l	153			Change=	3.48,				
					115–337.5 nmol/l	163			Change=	3.16,				
		Change in Timed up and go (TUG) (men)			10–90 nmol/l	114			Change=	-1.11,	+1.94	NC	0.99	
					92.5–102.5 nmol/l	86			Change=	-1.75,				
					105–120 nmol/l	110			Change=	0.69,				
					122.5–262.5 nmol/l	99			Change=	-3.05,				
		Change in Timed chair stands (TCS)(women)			10–80 nmol/l	159			Change=	16.28,	+14.28	NC	0.002	
					82.5–97.5 nmol/l	181			Change=	2.70,				
					100–112.5 nmol/l	153			Change=	3.51,				
					115–337.5 nmol/l	163			Change=	2.58,				
			7.70	12.62	Reference	Reference								

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Houston, 2012 ¹⁹² Healthy, Aging and Body Composition US Pittsburgh, Memphis		Change in Timed chair stands (TCS)(men)	1°	4y	10–90 nmol/l	114			Change= 3.36	-1.11, 7.82	+1.94	NC	0.99	B
					92.5–102.5 nmol/l	86			Change= 3.52	-1.75, 8.79				
					105–120 nmol/l	110			Change= 4.95	0.69, 9.21	+3.53	NC		
					122.5–262.5 nmol/l	99			Change= 1.42	-3.05, 5.09				
	knee extensor strength	1°	4y	<50 nmol/L	1818	nm/ kg	12.83	Final=11.9	SE=0.2	NC	NC	0.76		
				50–<75 nmol/L			13.01	Final=11.9	SE=0.2					
				≥75 nmol/L			12.91	Final=11.8	SE=0.2					
				grip strength	1°	4y	<50 nmol/L	1971	kg	28.87	Final=29.2	SE=0.4	NC	
	50–<75 nmol/L	29.71	Final=29.8				SE=0.4							
	≥75 nmol/L	29.81	Final=30.0				SE=0.4							

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality	
Menant, 2012 ¹⁹³ Sydney, Australia		Primary-Grip strength	1°	1 y	> 50 nmol/l	309	kg	NR	final= 28.7	SD=11.7	+4.7	3.3, 6.1	<0.001	B	
					≤ 50nmol/l	154	kg		final= 24.0	SD=10.3	Reference				
		Primary- Quadriceps strength			> 50 nmol/l	309	kg		final= 28.9	SD=11.9	+6	5, 7			
					≤ 50nmol/l	154	kg		final= 22.9	SD=10.4	Reference				
		Primary-Finger press reaction time			> 50 nmol/l	309	ms		final= 235.4	SD=45.2	-11.7	NR			
					≤ 50nmol/l	154	ms		final= 247.1	SD=50.0	Reference				
		Primary-Sway, eyes open-floor			> 50 nmol/l	309	mm2		final= 76.5	SD=40.1	-5.4	-11.0, 0.2			0.06
					≤ 50nmol/l	154	mm2		final= 81.9	SD=46.0	Reference				
		Primary-Sway, eyes open-foam			> 50 nmol/l	309	mm2		final= 182.2	SD=97.5	-5.6	-17.7, 6.5			0.37
					≤ 50nmol/l	154	mm2		final= 187.8	SD=89.9	Reference				
		Primary- Physiological Profile assessment (PPA) fall risk score			> 50 nmol/l	309			final= 0.8	SD=0.9	-0.2	-0.3, -0.1			<0.001
					≤ 50nmol/l	154			final= 1.0	SD=0.9	Reference				
		Primary-Maximal balance range			> 50 nmol/l	309	mm		final= 155.7	SD=56.8	+21.1	14.2, 28.0			<0.001
					≤ 50nmol/l	154	mm		final= 134.6	SD=49.7	Reference				
		Primary- Coordinated stability score			> 50 nmol/l	309			final= 13.6	SD=12.4	-5.0	-7, -3			<0.001
					≤ 50nmol/l	154			final= 18.6	SD=13.3	Reference				
		Primary-Choice stepping reaction time			> 50 nmol/l	309	secs		final= 987.4	SD=215.1	-73.4	-101.7, - 45.1			<0.001
					≤ 50nmol/l	154	secs		final= 1060.8	SD=223.0	Reference				
		Primary-6 m walk speed			> 50 nmol/l	309	m/s		final= 0.73	SD=0.16	+0.06	0.04, 0.08			<0.001
					≤ 50nmol/l	154	m/s		final= 0.67	SD=0.17	Reference				

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Scott, 2010 ¹⁹¹ Tasmanian Older Adult Cohort Study (TASOAC) Tasmania, Australia		Appendicular lean mass	1°	2.6 y	> 50nmol/l	389	perce nt	62.20	NR	NR	+0.01	-0.52, 0.54	0.963	B
					≤ 50nmol/l	297	perce nt	59.30	NR	NR	Reference			
		Leg strength			> 50nmol/l	389	kg	100.80	NR	NR	+5.74	0.65, 10.82	0.027	
					≤ 50nmol/l	297	kg	91.50	NR	NR	Reference			
		Leg muscle quality			> 50nmol/l	389	kg/kg	5.90	NR	NR	+0.49	0.17, 0.82	0.003	
					≤ 50nmol/l	297	kg/kg	5.50	NR	NR	Reference			

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)		Hip fracture	1°	11 yrs	Normal level	118	1126	HR	1.00	Reference	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	72	495		1.34	0.97, 1.84		
Barbour, 2012 ¹⁹⁴ US Pittsburgh, PA and Memphis, TN	age 70–79	Hip fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	84	2501	HR	1.92	0.97, 3.83	0.217	B
					Quartile 2: 44.5–60.9 nmol/L				0.75	0.32, 1.72		
					Quartile 3: 60.9–79.9 nmol/l				1.86	1.00, 3.45		
					Quartile 4: >79.9 nmol/l				1.00	Reference		
		nonspine fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	247	2494	HR	1.21	0.83, 1.75	0.752	
					Quartile 2: 44.5–60.9 nmol/L				1.01	0.68, 1.49		
					Quartile 3: 60.9–79.9 nmol/l				1.12	0.78, 1.60		
					Quartile 4: >79.9 nmol/l				1.00	Reference		
Barrett-Connor, 2012 ¹⁹⁸ US (various)	51–70 yrs; ≥71 yrs	nonspine fracture	1°	4.6 yrs	Normal level	100	594	HR	1.2	0.8, 1.8		A
					Low vit D	34	183		1.00	Reference		
Burgi 2011 ²⁰³ US	9–50 yrs	stress fracture	1°	NR	3.75–49.25 nmol/L	600	1200	OR	1.00	Reference	0.02	B
					49.5–66.5 nmol/L				0.77	0.54, 1.11		
					66.8–82 nmol/L				0.76	0.52, 1.10		
					82.3–99.5 nmol/L				0.61	0.42, 0.91		
					99.75–281.25 nmol/L				0.51	0.34, 0.78		

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Cauley 2011 ¹⁹⁹ WHI OS US	Post- meno- pausal women	fractures	1°	8.6 yrs	<50 nmol/L	150	270	OR	1.00	Reference	0.02	A
whites					50– <75 nmol/L	156	321		0.82	0.58, 1.16		
					≥75 nmol/L	84	189		0.56	0.35, 0.90		
					<50 nmol/L	241	508	OR	1.00	Reference	0.043	
blacks					50– <75 nmol/L	108	193		1.48	1.05, 2.10		
					≥75 nmol/L	30	57		1.33	0.73, 2.43		
Hispanics					<50 nmol/L	89	182	OR	1.00	Reference	0.72	
					50– <75 nmol/L	71	140		1.02	0.69, 1.79		
					≥75 nmol/L	31	60		1.09	0.50, 2.37		
Asians					<50 nmol/L	37	80	OR	1.00	Reference	0.22	
					50– <75 nmol/L	45	85		1.49	0.76, 2.93		
					≥75 nmol/L	30	59		1.66	0.68, 4.02		
native Americans					<50 nmol/L	29	55	OR	1.00	Reference	0.29	
					50– <75 nmol/L	9	18		0.64	0.15, 2.79		
					≥75 nmol/L	6	15		0.43	0.09, 2.08		
Rouzi, 2012 ²⁰⁰ Jeddah, Saudi Arabia		fragility fractures	1°	5.2 yrs	<17.90 nmol/L	138	707	OR	1.25	0.91, 1.70		A
					>45.1 nmol/L				1.00	Reference		
Cauley, 2008 ¹⁹⁵ WHI-OS nd		hip fractures	1°	7.1 yrs	Quartile 1: 9.2–47.5 nmol/L	NR	244	OR	1.71	1.05, 2.79	0.015	A
	Quartile 2: 47.6–70.6 nmol/L				NR	195	1.09		0.70, 1.71			
	Quartile 3: 60.2–70.6 nmol/L				NR	167	0.82		0.51, 1.31			
	Quartile 4: 70.7–121.5 nmol/L				NR	193	1.00		Reference			
	per 2.5 nmol/L decrease				NR	799	1.03		1.01, 1.05			
	per 25 nmol/L decrease				NR	799	1.33		1.06, 1.68			
Looker 2013 ¹⁹⁶ NHANES III		major osteoporotic fracture	1°	7 yrs	per 1 SD unit decline in serum 25OHD	400	4749	RR	1.27	1.12, 1.44		A
						212	NR		1.14	0.97, 1.34		
						188	NR		1.40	1.13, 1.74		

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Holvik 2013 ¹⁹⁷ Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)		hip fracture	1°	10.7 yrs	Q1: 4.5–42.1	317	256	HR	1.34	1.05, 1.70		A
					Q2: 42.2–53.5	294	255		1.13	0.90, 1.44		
					Q3: 53.5–67.8	272	255		1.10	0.87, 1.39		
					Q4: 67.9–250.0	279	256		1.00	Reference		
Menant, 2012 ¹⁹³ Sydney, Australia		Primary- Falls in men	1°	1 y	≤ 50nmol/l	94	215	IRR	1.93	1.19, 3.15	0.008	B
					> 50nmol/l			IRR	1.00	Reference		
		Primary- Falls in women			≤ 50nmol/l	115	248	IRR	0.83	0.56, 1.23	0.362	
					> 50nmol/l			IRR	1.00	Reference		
Michael, 2011 ¹⁸⁹ US (various)		Primary- Physical performance summary score	1°	6 y	≥ 75 nmol/l	NR	64	RR	3.66	1.88, 5.45	<0.001	A
					50–74nmol/l	NR	148	RR	2.32	0.89, 3.75		
					25–49 nmol/l	NR	255	RR	1.64	0.28, 3.01		
					≤ 25 nmol/l	NR	67	RR	1	Reference		

Vitamin D and All-Cause Mortality

Synopsis

The current report identified 25 cohort studies that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, seven found no association (rated 1A, 6B), 16 found an association of lower 25(OH)D concentrations with increased risk for mortality (rated 6A, 9B: one article reported on two studies), and two reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk (rated A and B).

The assessment of the literature on vitamin D and all-cause mortality in the original report was based on a reanalysis of 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% 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)

The current report identified 25 observational studies that assessed the association between serum 25(OH)D concentrations and all-cause mortality as an outcome. None of the outcomes fit the criteria needed to be included in the meta-analysis that was conducted for the original report and are described below. As mentioned in the Methods section, the original report updated and reanalyzed published meta-analyses of mortality outcomes. That report drew its own conclusions based on its analyses. The original report also commented on the concordance of its conclusions with those of the published meta-analyses.

Relevant Published Systematic Reviews of RCTs (With Meta-Analyses)

The original report identified two systematic reviews (with meta-analyses) of RCTs that summarized the effect of vitamin D supplementation with or without calcium on mortality.^{204,205} One systematic review (Avenell 2008) examined only trials on fall prevention, and briefly described results on mortality.²⁰⁵ The second meta-analysis (Autier 2007) focused specifically on mortality.²⁰⁴ It included all RCTs identified in the first, as well as additional trials (which were

ⁱNumerical data were extracted from previous systematic reviews—no additional studies were identified. For this reason, we did not appraise studies for their methodological quality.

not eligible for the primary analysis of the Avenell 2008 systematic review, namely prevention of falls).²⁰⁴ 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.

Table 37. Summary of systematic review on vitamin D supplementation and all-cause mortality (not updated from original report)

Not updated from original report

Author Year [PMID]	Autier 2007 ²⁰⁴ [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 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)

No RCTs were identified for the current report that assessed the effect of vitamin D or vitamin D and calcium supplementation on risk for all-cause mortality. For the original report, Lyons 2007 (n=3343, 24% males) used monthly supplementation with 100,000 IU of vitamin D₂, orally for 3 years.¹⁸⁵ 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

For the re-analysis conducted in the original report, they excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,²⁰⁶ one was published only in abstract form,²⁰⁷ in one trial the controls also received supplementation with vitamin D, albeit with a smaller dose,²⁰⁸ and two trials used vitamin D injections.^{209,210} One additional eligible RCT (Lyons 2007)¹⁸⁵ 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% CI 0.92, 1.02), with no evidence for between-study heterogeneity ($P=0.39$, $I^2=0\%$).

Cohort Studies

The current report identified 25 cohort studies (one article reported on two studies, and one study was reported in two articles) that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, six found no association (rated 1 rated A, 6 rated B).^{58,70,77,79,83,98,144} These studies ranged in length of followup from 3 to 24 years. Sixteen found an association of lower 25(OH)D concentrations with increased risk for mortality (6 rated A, 9 rated B: one article reported on two studies);^{60,73-77,81,86,87,101,211-218} most associations were small, limited to a particular subgroup, or limited to the first 3 years after baseline measurement.²¹¹ Two studies reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk, that is a j-shaped association (rated A and B).^{84,218} A 15-year followup assessment of 15,099 NHANES participants (age 20 and older) reported the lowest association with all-cause mortality at a 25(OH)D concentration of 81 nmol/L. For 25(OH)D concentrations less than 20nmol/L, the RR for all-cause mortality was 2.2 (95% CI 1.6, 2.9) and for 25(OH)D concentrations greater than 120nmol/L, the RR was 1.5 (95% CI 1.02, 2.30).²¹⁸ These same associations were seen for both men and women, for adults 20 to 64 years of age and for non-Hispanic whites.

The original report identified four prospective cohort studies described in 5 publications.^{85,219-222} The characteristics of the four cohorts are shown in Table 38. One was rated “B”²¹⁹ for methodological quality and the remaining were rated “C.”

Table 39 summarizes the findings of the four studies. Briefly, only Jia 2007²¹⁹ 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 2008⁸⁵ 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 15-year followup analysis of NHANES III data identified for the current report observed a j-shaped association of serum 25(OH)D concentrations with all-cause mortality for adults 20 to 64 years of age, with serum concentrations less than 30 nmol/L and greater than 120nmol/L associated with a higher risk. A subgroup

analysis of people younger than 65 years in NHANES III **identified for the original report** (Melamed 2008) found no significant associations between 25(OH)D concentrations and all-cause mortality.

- **51–70 y**

The current report identified one study that observed a significant association of serum 25(OH)D concentrations and all-cause mortality among adults 50 to 74 years of age.

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% CI 0.92, 1.02), with no evidence for between-study heterogeneity ($p=0.39$, $I^2=0\%$). 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**

Of three cohort studies identified for the current report that assessed the association between serum 25(OH)D and all-cause mortality, one in men who were 85 years old at baseline, one in individuals 70 to 88 years old followed up to 9.2 years, and the third in individuals who were 77 years old at baseline, one reported no association and two observed an association between lower serum 25(OH)D concentrations and increased all-cause mortality. For studies identified for the original report, 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 (updated from original report)

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 ²¹⁹ UK (57°N) [17442130]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Not terminally ill or demented >75 52	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA ND	Comparison of various 25(OH)D concentration categories		X		X	X	X
Sambrook 2004 & 2006 ^{220,221} FREE ^A Australia (33°S) [15531500 & 16598375]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Not bedridden >65 22	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Dia-sorin) ND	Association with log 25(OH)D		X		X		
Visser 2006 ²²² Longitudinal Aging Study Netherlands (52°N) [16960177]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	General population ^B >65 51	<ul style="list-style-type: none">• Assay method• Season blood drawn	Competitive protein binding ND	Comparison of various 25(OH)D concentration categories		X	X			X
Melamed 2008 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Age mean (range), y• Male (%)	General population 45 (≥20) 46	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Dia-sorin) ND	Comparison of various 25(OH)D concentration categories	X	X	X	X	X	X
NEW Studies											
Bolland 2010 ⁵⁸ New Zealand	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Healthy Post-menopausal 74 (SD 4.2) 0%			Comparison of various 25(OH)D concentration categories		X	X	X		X
Cawthon 2010 ⁹⁸ MrOS (multisite) US	<ul style="list-style-type: none">• Health status• Mean age (Age range), y• Male (%)	>80% Excellent/good health status 74 (> or =65) nd			Association with log 25(OH)D	X	X	X	X	X	X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure Lifestyle
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 74 (SD 4.6) 30%	Comparison of various 25(OH)D concentration categories		X	X	X		X
Eaton 2011 ⁷⁰ WHI substudy US (multisite)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 65.1 (SD 7.6) 0%	Post-menopausal women 50–79 years stratified by 25(OH)D quartiles			X	X	X	X
Fedirko 2012 ¹⁰¹ EPIC US (4 sites)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 62.1 (4.2) 40.5%	Diagnosis at age of 62 stratified by 25(OH)D quintiles		X	X	X	X	X
Hutchinson 2010 ⁷⁹ Tromsø Study Tromsø, Norway	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	Nd nd nd	Smoking and non-smoking cause of death stratified by 25(OH)D quartiles		X	X	X		X
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living Well (WHEL) Study	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Cancer in remission 51.9 (SD 9) 0%	Breast cancer survivors stratified by 25(OH)D concentration categories						
Johansson 2012 ²¹¹ MrOS Sweden: Gothenburg, Malmö, Uppsala	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Some with diabetes, htn, cancer, stroke, MI, angina 75.7 (SD 3.4) 100%	Death and mortality stratified by varying 25(OH)D concentration levels		X		X		X
Kestenbaum 2011 ⁸¹ Cardiovascular Health Study US (various)	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	nd 73 (SD 4) 42%	All-cause mortality stratified by 25(OH)D quartiles						

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure Lifestyle
Kritchevsky 2012 ²¹² Health, Aging, and Body Composition (ABC) Study US Pittsburgh, Memphis	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Well-functioning 74.7 (SD 2.9) 49%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Lin 2012 ⁸³ General Population Trial of Linxian, China	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Healthy, Hypertension 56.5 (7.9) 55%	All-cause mortality stratified by continuous 25(OH)D		X	X	X		X
Michaelsson 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	More than 1/3 being treated for hypertension 71 (0.6) 100%	Overall mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Pilz 2009 ⁷³ Hoorn Study Netherlands	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	More than 20% Type 2 Diabetes or impaired glucose tolerance 69.2 (6.5) 50%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Semba 2010 ⁹³ InCHIANTI Italy	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	Nd 78 (72–85) 67.3%	All-cause mortality and cardiovascular mortality stratified by 25(OH)D quartiles		X	X		X	X
Signorello 2013 ⁷⁴ Southern Community Cohort Study US	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	nd nd nd	All-cause mortality stratified by 25(OH)D quartiles			X			X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure Lifestyle
Smit 2012 ²¹³ NHANES III US (various)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Malnourished/frailty, pre-frail, not frail 69.4 (SD 0.3) 46.5%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Szulc 2009 ²¹⁴ MINOS Study Montceau les Mines, France	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 64 (SD 7) 55%	Mortality stratified by 25(OH)D quartiles	X	X	X	X		X
Szulc 2009 ²¹⁵ MINOS Study Montceau les Mines, France	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 64 (SD 7) 100%	Mortality stratified by 25(OH)D quartiles		X	X	X		X
Virtanen 2011 ²¹⁶ Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	Post-menopausal, 54–62% hypertension 61.8 (53.4–72.7/SD 6.2) 48.6%	Overall mortality stratified by 25(OH)D tertiles		X	X	X		X
Welsh 2012 ⁶⁰ MIDSPAN Family Study Renfrew and Paisley, UK	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	vitamin D not deficient 45.2 (6.2) 46%	All-cause mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Tomson 2013 ⁷⁵ Whitehall study London, UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%	Death (all non-vascular) and Death (all causes) stratified by 25(OH)D doubling concentration			X	X		X
Skaaby 2013 ⁸⁶ Monica10 and Inter99 Denmark	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR Monica 10: 55.4 Inter 99: 46.1 Monica 10: 50.2 Inter 99: 49.2	All-cause mortality stratified by 25(OH)D quartiles		X		X	X	X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV	Exposure Lifestyle
Wong 2013 ²¹⁷ Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 76 (70–88) 100%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X		X
Sempos 2013 ²¹⁸ NHANES III US	<ul style="list-style-type: none"> • Health status • Mean age (SE), y • Male (%) 	NR 45 (SE 0.47) 49%	All-cause mortality stratified by 25(OH)D in 9 categories		X			X	
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 62 (SD 6.5) 43.8%	All-cause mortality stratified by 25(OH)D tertiles	X	X		X	X	X
Formiga 2014 ⁷⁷ Octabaix Spain	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Oldest old 85 (SD 0) 39.4%	Total mortality stratified by 25(OH)D quartiles		X		X		

^AFracture Risk Epidemiology in the Elderly

^B~40% with CVD and ~60% arthritis

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report)

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 ²¹⁹ 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	1.4	0.73, 2.70		
					30.1–37.0 (M)/ 24.1–30.2 (F)	21	80	0.9	0.45, 1.79		
					37.1–47.0 (M)/ 30.3–39.0 (F)	17	78	0.8	0.39, 1.62		
					47.1–82.0 (M)/ 39.1–82.0 (F)	16	79	1	Reference		
Sambrook 2004 & 2006 ^{220,221} 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 ²²² 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	0.72, 1.40		
					50–74.9	30	440	0.91	0.65, 1.26		
					≥75	29	231	1	Reference		
Melamed 2008 ⁸⁵ 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	Reference		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Table for Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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 ⁸⁵ 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	Reference			
Melamed 2008 ⁸⁵ 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	Reference			
Melamed 2008 ⁸⁵ 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	Reference			
Melamed 2008 ⁸⁵ 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	Reference			
NEW studies												
Bolland 2010 ⁵⁸ New Zealand	Post-menopausal women	Primary- Death	5 yrs	25(OH)D	<50 nmol/L	13	373	HR=0.90	0.4, 2.0	0.82	A	
					≥50 nmol/L	16	366	1.00	Reference			
Cawthon 2010 ⁹⁸ MrOS (multisite) US	Men (51-70 yrs; ≥71 years)	all-cause mortality	7.3 yrs	25(OH)D	Quartile 1: <49.75 nmol/L		372	HR=0.95	0.68, 1.34	0.961	B	
					Quartile 2: ≥49.75 to <63.0 nmol/L		370	1.05	0.75, 1.47			
					Quartile 3: ≥63.0 to <75.0 nmol/L		372	0.89	0.64, 1.24	0.706		
					Quartile 4: ≥75.0		376	1.00	Reference			
					Deficient, <50 nmol/L		376	0.94	0.67, 1.32			
					Insufficient, 50 to <75 nmol/L		737	0.97	0.72, 1.30			
					Sufficient, ≥75 nmol/L		377	1.00	Reference			
					per SD decrease			1.01	0.89, 1.14			

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	White older adults	Death	11 yrs	25(OH)D	Normal level	539	1126	HR=1.00	Reference	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	287	495	1.32	1.14, 1.53		
Eaton 2011 ⁷⁰ WHI substudy US (multisite)	Post-menopausal women 50–79 years	all-cause mortality	10 yrs	25(OH)D	Quartile 1: 3.25–36.50 nmol/L		608	HR=1.25	0.80–1.95	0.39	A
					Quartile 2: 36.51–49.95 nmol/L		606	1.13	0.73–1.75		
					Quartile 3: 49.96–65.38 nmol/L		608	1.17	0.75–1.81		
					Quartile 4: 65.39–146.67 nmol/L		607	1.00	Reference		
Fedirko 2012 ¹⁰¹ EPIC US (4 sites)	Men and women (diagnosed at an average age of 62)	overall mortality	73 mos	25(OH)D	<36.3	128	242	HR=1.00	Reference	<0.01	B
					36.4–48.6	108	239	0.82	0.63, 1.07		
					48.7–60.5	117	241	0.91	0.70, 1.18		
					60.6–76.8	95	240	0.78	0.59, 1.03		
					>76.8	93	240	0.67	0.50, 0.88		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Hutchinson 2010 ⁷⁹ Tromsø Study (Norway)	Men(55–74 yrs) Women (50–74 yrs)	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	247	1184	HR=1.32	1.07–1.62	NR	B
					Quartile 2: mean=46.7 (sd=6.0)	198	1187	1.06	0.86–1.31		
					Quartile 3: mean=56.2 (sd=6.0)	190	1192	1.09	0.88–1.34		
					Quartile 4: mean=72.3 (sd=13.2)	163	1188	1.00	Reference		
	nonsmokers	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	156	597	1.06	0.83–1.35	NR	
					Quartile 2: mean=46.7 (sd=6.0)	143	606	0.97	0.76–1.25		
					Quartile 3: mean=56.2 (sd=6.0)	138	607	1.04	0.81–1.33		
					Quartile 4: mean=72.3 (sd=13.2)	124	600	1.00	Reference		
smokers				Insufficient, <50 nmol/L	164		1.13	0.72, 1.79	0.59		
				Sufficient, ≥50 nmol/L	336		1.00	Reference			
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living Well (WHEL) Study	Breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 years	mortality	7.3 yrs	25(OH)D							B
Johansson 2012 ²¹¹ MrOS (Sweden)	Men (70–81 yrs)	death	8.2 yrs	25(OH)D	per SD decrease	577	2878	HR=1.16	1.06, 1.26	NR	A
Kestenbaum 2011 ⁸¹ Cardiovascular Health Study	>65 years	Primary- all-cause mortality	14 yrs	25(OH)D	>75 nmol/L	329	681	HR=1.00	Reference	0.012	B
					37.5–75.0 nmol/L	668	1247	1.15	1.00, 1.33		
					<37.5 nmol/L	229	384	1.29	1.05, 1.57		
					continuous per 25 nmol/L	1226	2312	1.09	1.02, 1.17		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Kritchevsky 2012 ²¹² Health, Aging, and Body Composition (ABC) Study	Older community dwelling men and women (70–79 yrs)	all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	44	108	HR=2.27	1.59, 3.24	<0.001	B
					25 to <50 nmol/L	241	750	1.48	1.20, 1.84		
					50 to <75 nmol/L	229	931	1.25	1.02, 1.52		
					≥75 nmol/L	177	849	1.00	Reference		
	whites	all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	10	25	2.02	1.02, 3.99	0.001	
					25 to <50 nmol/L	82	279	1.54	1.16, 2.06		
					50 to <75 nmol/L	138	620	1.22	0.96, 1.55		
					≥75 nmol/L	143	691	1.00	Reference		
	blacks	all-cause mortality	8.5 yrs	25(OH)D	<25 nmol/L	34	83	2.59	1.57, 4.26	<0.001	
					25 to <50 nmol/L	159	471	1.76	1.20, 2.57		
					50 to <75 nmol/L	91	311	1.60	1.07, 2.39		
					≥75 nmol/L	34	158	1.00	Reference		
Lin 2012 ⁸³ General Population Trial of Linxian (China)						793	1101	HR=1.01	0.97, 1.05	0.735	B
	Men 40–69 yrs	all-cause mortality	24 yrs	25(OH)D	continuous 25(OH)D	479	608	0.99	0.94, 1.04	0.7	
	Women 40–69 yrs					314	493	1.03	0.97, 1.10	0.348	
Michaelsson 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala (Sweden)	Elderly men birth 1920–1924	overall mortality	12.7 yrs	25(OH)D	< 10th percentile (<46 nmol/L)	76	119	HR=1.43	1.11, 1.84		B
					10th–90th percentile (46–93 nmol/L)	444	956	1.00	Reference		
					>90th percentile (>93 nmol/L)	64	119	1.27	0.97, 1.66		
Pilz 2009 ⁷³ Hoorn Study Netherlands	Men and women (50–75 yrs)	all-cause mortality	6.2 yrs	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	21	152	HR=1.97	1.08, 3.58	0.027	B
					2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	30	462	1.00	Reference		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Semba 2010 ⁹³ InCHIANTI Italy		all-cause mortality	6.5 yrs	25(OH)D	1st quartile: <26.3 nmol/L	NR	252	HR 2.11	1.22, 3.64		
					2nd quartile: 26.3–40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.3–64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		
					Quartile 4: (>54.1nmol/L)	364	827	1.00	Reference		
Signorello 2013 ⁷⁴ Southern Community Cohort Study US	Men and women (40–79 yrs)	all-cause mortality	1 yr or more	25(OH)D	Quartile 3: (37.9–54.1 nmol/L)	405	868	1.17	0.95, 1.45	<0.001	
					Quartile 2: (25.5–37.9 nmol/L)	482	945	1.41	1.14, 1.74		
					Quartile 1: <25.5 nmol/L)	601	1064	1.80	1.43, 2.27		
					Quartile 4: (>54.1nmol/L)	181	400	1.00	Reference		
					Quartile 3: (37.9–54.1 nmol/L)	266	565	1.15	0.87, 1.53		
					Quartile 2: (25.5– 37.9nmol/L)	353	730	1.19	0.91, 1.57		
	African Americans	all-cause mortality	1 yr or more	25(OH)D	Quartile 1: <25.5 nmol/L)	475	855	1.60	1.20, 2.14	<0.001	A
					Quartile 4: (>54.1nmol/L)	179	419	1.00	Reference		
					Quartile 3: (37.9–54.1 nmol/L)	136	296	1.09	0.78, 1.52		
					Quartile 2: (25.5–37.9 nmol/ L)	129	214	1.99	1.37, 2.90		
					Quartile 1: <25.5 nmol/L)	122	203	2.11	1.39, 3.21		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Smit 2012 ²¹³ NHANES III	Adults (60 and over)	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	2.98	2.01, 4.42		A
					Quartile 2: 49.5–66.4 nmol/l	NR	NR	2.37	1.44, 3.89		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	2.50	1.48, 4.21		
					Quartile 4: >84.1 nmol/l	NR	NR	1.43	0.83, 2.46		
	frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.97	1.61, 2.40		
					Quartile 2: 49.5–66.4 nmol/l	NR	NR	1.62	1.29, 2.03		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	1.51	1.16, 1.97		
					Quartile 4: >84.1 nmol/l	NR	NR	1.82	1.41, 2.35		
	pre-frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.25	0.97, 1.60		
					Quartile 2: 49.5–66.4 nmol/l	NR	NR	1.20	0.96, 1.49		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	1.11	0.88, 1.40		
					Quartile 4: >84.1 nmol/l	NR	NR	1.00	Reference		
Szulc 2009 ²¹⁴ MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	per SD decrease	600	782	1.22	1.01, 1.48	<0.05	A
					Quartile 1 <65 nmol/l summer or <40 nmol/l other months	NR	NR	1.44	1.03, 2.03		
					Quartiles 2–4	NR	NR	1.00	Reference		
Szulc 2009 ²¹⁵ MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	Quartile 1	NR	NR	1.6–1.8	NR	<0.05	A
					Quartiles 2–4	NR	NR	1.00	Reference		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Virtanen 2011 ²¹⁶ Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	Men (average age 61.8)	mortality	9.1 yrs	25(OH)D	Tertile 1: 8.9–34.0 nmol/L	39	379	2.06	1.12, 3.80	0.02	A
					Tertile 2: 34.1–50.8 nmol/L	31	378	1.68	0.92, 3.07		
					Tertile 3: 50.9–112.8 nmol/L	17	379	1.00	Reference		
Welsh 2012 ⁶⁰ MIDSPAN Family Study Scotland	Men and women	Primary- all-cause mortality	14.4 yrs	25(OH)D	per 1 SD increase	70	1492	0.74	0.56, 0.99		B
					Deficient, <37.5 nmol/L	NR	689	2.02	1.17, 3.51		
					Not deficient ≥37.5 nmol/L	NR	803	1.00	Reference		
Tomson 2013 ⁷⁶ Whitehall study		Death, all non- vascular	13.1 yrs	25(OH)D	Doubling Concentration	1857	5409	0.77	0.69, 0.86		B
		Death, all causes				3215	5409	0.78	0.72, 0.85		
Skaaby 2013 ⁸⁶ Monica10 and Inter99		all-cause mortality	10 yrs	25(OH)D	per 10nmol/L	633	8329	0.95	0.92, 0.99	0.005	B
					Q1			1.00	Reference		
					Q2			0.79	0.64, 0.98		
					Q3			0.81	0.65, 1.01		
					Q4			0.73	0.57, 0.92		
Wong 2013 ²¹⁷		all-cause mortality	6.7 yrs	25(OH)D	per 10nmol/L decrease in	1144	4203				B
					25(OH)D			1.04	1.01, 1.07		
					halving of 25(OH)D			1.21	1.08, 1.35		
					Q1: 10–52.8			1.20	1.02, 1.42		
					Q2: 52.9–67.3			1.00	Reference		
					Q3: 67.4–81.6			0.99	0.84, 1.17		
					Q4: 81.7–238.4			0.99	0.83, 1.17		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (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
Sempos 2013 ²¹⁸ NHANES III		death from all- cause	15 yrs	25(OH)D	<20 20–29 30–39 40–49 50–59 60–74 75–99 100–119 ≥120	79 297 592 694 668 775 533 110 36	251 1270 2340 2790 2526 3046 2156 518 202	1.6 1.5 1.3 1.1 1.2 1.1 1.0 1.1 1.4	1.2, 2.2 1.2, 1.8 1.1, 1.5 0.96, 1.3 1.01, 1.30 0.99, 1.30 Reference 0.9, 1.4 0.9, 2.2		A
Schottker 2013 ⁷⁶ ESTHER											
	≥65 yrs of age	all-cause mortality	9.5 yrs	25(OH)D	<30 30–50 >50 <30 30–50 >50	238 448 397 142 269 236	1444 4199 3935 609 1706 1394	1.68 1.17 1.00 1.41 1.09 1.00	1.41, 2.01 1.01, 1.35 Reference 1.13, 1.77 0.90, 1.31 Reference		B
	<65 yrs of age				<30 30–50 >50	238 448 397	835 2493 2541	2.08 1.30 1.00	1.58, 2.76 1.04, 1.63 Reference		
Formiga 2014 ⁷⁷ Octabaix		total mortality	2.8 yrs	25(OH)D	Q1: <34.94 Q2: 34.94–61.65 Q3: 61.66–83.37 Q4: >83.37	15 18 11 14	71 77 84 80	1.28 1.36 0.76 1.00	0.61, 2.6 0.67, 2.74 0.34, 1.68 Reference	0.41	B

^AFracture Risk Epidemiology in the Elderly

^BPer 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 large prospective cohort study identified for the current report that evaluated the association between serum 25(OH)D concentration and the risk for hypertension using the Intermountain database found a highly significant association of very low and low baseline serum 25(OH)D concentrations and the prevalence of hypertension at an average of 1.3 years followup. An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians’ Health Study at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association.** A combined analysis of a small subset of the Health Professionals Followup (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)

A prospective cohort study identified for the current report analyzed records of 19,128 patients, age 50 and over, in the Intermountain Database for which baseline serum 25(OH)D concentrations were available (25% male) (rated C). Those with serum 25(OH)D concentrations less than 37.5 nmol/L and between 40 and 75 nmol/L were significantly more likely than those with normal serum 25(OH)D concentrations (>75 nmol/L) (HR 1.62, HR 1.18, respectively) to have hypertension within an average followup time of 1.3 years. No subgroup analyses were done by sex or age.²²³ An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians’ Health Study (men of mean age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile (rated A).²²⁴

One analysis (methodological quality B) **identified for the original report** 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.²²⁵ 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.²²⁶ 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 Intermountain data were analyzed with 25(OH)D cutpoints of 37.5 and 75 nmol/L. Significant associations were identified for those with serum concentrations below 75 nmol/L. 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**
Individuals 50 and over with serum 25(OH)D concentrations less than 75nmol/L, identified in the Intermountain Health Database for the current study, had higher prevalence of hypertension at 1.3 years (average) followup. No subgroup analysis was conducted to further assess individuals over 70 or risk by sex. An assessment of the association between serum 25(OH)D and incident hypertension in men in the Physicians' Health Study (mean age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile. HPFS and NHS included participants mostly within this life stage. In men and women, the study found higher incidence of hypertension at 4 years follow up 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 follow up.
- **Pregnant & lactating women**
Not reviewed

Table 40. Vitamin D and hypertension: Characteristics of cohort studies (updated from original report)

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 ²²⁵ HPFS, NHS US (various) [17372031]	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Any Men 65 (8) Women 57 (7) 34	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)		X	X			X	
Forman 2008 ²²⁶ NHS 2 US (various) [18838623]	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	No HTN, CVD, DM, obesity, cancer 43 (40–46) 0	<ul style="list-style-type: none">• Assay method• Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)	X	X	X		X		
NEW Cohort Study												
Anderson 2010 ²²³ US	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 55 (21) 25.2%	<ul style="list-style-type: none">• Assay method• Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)							
Wang 2013 ²²⁴ Physicians' Health Study (PHS) US	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy 57.6 (SD 7.6) 100%	<ul style="list-style-type: none">• Assay method• Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D quartiles	X	X	X			X	

Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report)

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, HR, RR	95% CI	P for Trend	Study Quality
Men											
Forman 2007 ²²⁵ 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*		
		≥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 ²²⁶ 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		

Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report) (continued)

Author Year Study Name [PMID]	Mean (SD) Age, Sex	Outcome	Followup Duration	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR, HR, RR	95% CI	P for Trend	Study Quality
Forman 2007 ²²⁵ 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	
		Hypertension (274/613; 0.229)	8 y	25(OH)D	≥37.5	118	nd	1	Reference		
					<37.5	20	nd ^A	1.7	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		
NEW Cohort Studies											
Anderson 2010 ²²³ US	19–50, 51–70 yrs	Hypertension	1.3 yrs on average	serum 25(OH)D	very low (Vit D level ≤37.5 nmol/L)	7848	15,121	HR= 1.62	1.38, 1.89	p<0.0001	B
					low (Vit D level 56– 75 nmol/L)	8530	19,474	1.18	1.05, 1.33	p=0.005	
					normal (Vit D level > 75 nmol/L)	2750	6,909	1			
Wang 2013 ²²⁴ Physicians' Health Study (PHS)		Hypertension	15.3 yrs	25(OH)D	Q1: 13.0–57.8	97	164	1.00	Reference	0.43	A
					Q2: 37.0–74.9	97	164	0.94	0.69, 1.27		
					Q3: 48.6–93.5	79	167	0.69	0.50, 0.96		
					Q4: 68.8–167.2	94	165	0.82	0.60, 1.13		
					<50	73	136	1.00	Reference	0.32	
					50–74	144	244	1.03	0.75, 1.42		
					75–99	93	178	0.79	0.56, 1.11		
					≥100	57	102	0.94	0.62, 1.40		
				1,25(OH)D	Q1: 29.9–79.3	87	162	1.00	Reference	0.16	
					Q2: 68.0–88.2	80	162	0.92	0.66, 1.27		
Q3: 80.8–101.8	95	165	1.12		0.82, 1.54						
Q4: 94.0–177.6	101	162	1.19		0.86, 1.63						

* 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. **The current study identified ten RCTs that assessed the effects of one or more dosage levels of vitamin D compared with placebo on blood pressure in adults. Dosages ranged from 125IU to 7000IU per day. Followup ranged from 3 months to one year. Participants included postmenopausal women, middle aged U.S. blacks, overweight young Chinese and Danish adults, healthy South Asian women residing in the UK, and healthy young women. Of the ten RCTs, no effect of vitamin D supplementation was observed in seven, vitamin D significantly decreased systolic blood pressure in two studies (both systolic and diastolic in one of those two), and in the tenth, systolic blood pressure actually increased slightly in the supplemented group.**

Three trials from Germany, UK, and India **identified for the original report** 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)

Of the ten RCTs identified for the current report, one RCT found a decrease in systolic blood pressure of 0.2mm Hg for every 25nmol/L increase in supplemental plasma vitamin D. This U.S. trial randomized 283 overweight and obese (but otherwise healthy) black adults, 44 to 59 years of age and 63% female, to 1000, 2000, or 3000 IU/day cholecalciferol or placebo for 3 months (study rated A). Supplementation did not affect diastolic blood pressure. The effect was greater for those with lower baseline 25(OH)D concentrations but did not differ by baseline blood pressure. No subgroup analysis was performed by sex or use of antihypertensives.²²⁷ One Spanish 16-week RCT that supplemented healthy young women (18 to 35 years of age) with 200 IU vitamin D per day found a decrease in both systolic blood pressure (compared with 8-week levels) and diastolic blood pressure (compared with baseline) (rated B).²²⁸ Eight RCTs reported no effect on or an increase in systolic blood pressure (three rated A, two rated B, and one rated C).²²⁹⁻²³⁶

In the original report, 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.²³⁷ During the winter, they were given either a one-time dose of vitamin D₃ (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.²³⁸ For 8 weeks, the women took either vitamin D₃ 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 D₃ supplementation 120,000 IU with placebo for 3 weeks in generally healthy but obese men without hypertension.⁹⁶ 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 D₃ 800 IU together with calcium significantly lowered systolic blood pressure more than calcium alone, but every other week vitamin D₃ 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. **None of the studies identified for the current report stratified by age or sex.** The study of older women **identified for the original report** found a significant decrease in systolic blood pressure with relatively low dose vitamin D, a higher dose study of similarly aged men and women found no effect on blood pressure, and the highest dose study of men mostly in their 40s found an increase in systolic blood pressure.

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 of black U.S. residents 44–59 years of age found significant decreases in systolic blood pressure with vitamin D supplementation. A study of Spanish women 18–50 years found significant decreases in both systolic and diastolic blood pressure with modest daily supplementation. Eight studies identified for the current report, including those of overweight Chinese young adults, ages 18 to 25 years, and overweight Norwegian adults, 21 to 70 years of age found no effect of vitamin D supplementation on blood pressure. 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 D₃ 800 IU and calcium carbonate 1200 mg compared with calcium carbonate 1200 mg alone.
- **Postmenopause**
A study identified for the current report of healthy postmenopausal women (60–70 years of age) reported no effect of vitamin D supplementation on blood pressure, although serum 25(OH)D concentrations varied significantly with season of blood draw. 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 (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments	
Scragg 1995 ²³⁷ Cambridge, UK (52°N) [7498100]	<ul style="list-style-type: none">• 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 ²³⁸ Lower Saxony, Germany (52°N) [11297596]	<ul style="list-style-type: none">• 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 ⁹⁶ New Delhi, India (28.5°N) [19125756]	<ul style="list-style-type: none">• 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 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Forman 2013 ²²⁷ Boston, MA	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 51 (44–59) 34.6%	Serum vitamin D- 39.3 (26.8–83.5 IQR) nmol/L	Vit D ₃ 100,000 IU/day Vs. Vit D ₃ 2000 IU/day Vs. Vit D ₃ 4000 IU/day Vs. placebo	96.6%	
Gepner 2012 ²²⁹ Madison, WI	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy Postmenopausal 63.9 (SD 3) 0%	Serum vitamin D- 78.3+/-26.5 nmol/L	Placebo Vs. Vit D ₃ 2500 IU/day	nd	
Jorde 2010 ²³⁰ Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Using blood pressure or lipid lowering medication Overweight/Obese 47.5 (SD 11.4) 35.8%	58.0 ± 21.1 nmol/L	DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day Vs. DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day Vs. PP (placebo)+500 mg calcium/day	Vitamin D/ placebo capsules 95%-DD group, 96%-DP group and 96%-PP group calcium tablets 82%, 84% and 83%, respectively.	
Wood 2012 ²³¹ Aberdeen, UK	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy Post-menopausal 63.9 (SD 2.3) 0%	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l	400 IU Vit D/day Vs. placebo	nd	

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Zhu 2013 ²³² Shanghai, China	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 20.3 (SD 0.8) 14.3%	Habitual Ca intake CaD group—426.5 +/- 152.2 mg/d Control group—392.1 +/- 141.1 mg/d	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day Vs. energy-restricted diet alone (control)	95.8% in the calcium+D group
Daly 2009 ²³³ Melbourne, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, obese 61.2 (SD 7.5) 100%	Serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23 nmol/l	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day Vs. control (no additional fortified milk) (400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day Vs. control (no additional fortified milk)	85 ± 21%
Salehpour 2012 ²³⁴ Tehran, Iran	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight, obese 38 (SD 8.1) 0%	Serum 25(OH)D Vit D group—36.8 +/- 30 nmol/l Placebo group—46.9 +/- 32 nmol/l	Vit D 25 µg/day Vs. placebo	nd
Witham 2013 ²³⁵ UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 39.4 (SD 11.8) 0%	<50 nmol/L	Vit d3 100,000 units Vs. placebo	nd

**Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report)
(continued)**

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Toxqui 2013 ²²⁸ Spain	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 26.5 (SD 3.8) 0%	Serum: D- placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L	vit d 200 IU/day Vs. placebo	>96%	
Wamberg 2013 ²³⁶	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight/obese 41.2 (18–50) (SD 6.8) 27%	34.6±10.3 nmol/L	7000 IU cholecalciferol vs. placebo	94±8%	

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/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Scragg 1995 ²³⁷ 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 ²³⁸ 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	-	-13.6, -1.2 ^A	0.02	B
					Ca carbonate 1200 mg	72		140.6	-5.7	nd				
Nagpal 2009 ⁹⁶ 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	-0.02, 8.0	0.06	B
					Placebo	36		124	-3.4	-5.8, - 1.0				

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

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
DIASTOLIC BLOOD PRESSURE														
Scragg 1995 ²³⁷ UK	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
[7498100]					Placebo	94		82	-1	-6.8, 4.8 ^A				
Pfeifer 2001 ²³⁸ Germany	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	0.1	B
[11297596]					Ca carbonate 1200 mg	72		82.6	6.9	nd				
Nagpal 2009 ⁹⁶ New Delhi, India	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
[19125756]					Placebo	36		77	-1.3	-3.2, 0.7				

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

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality						
NEW Studies																				
Forman 2013 ²²⁷ Boston, MA	19–50 yrs	DBP	1°	3 months	Vit D ₃ 1000 IU/day	68	mmHg	79.8	final= 78.0	se=1.6	-0.9 ^B	-5.7, 3.9	0.71	A						
					Vit D ₃ 2000 IU/day	73		77.6	final= 76.0	se=1.8	-2.9 ^B	-7.9, 2.1	0.26							
					Vit D ₃ 4000 IU/day	70		79.8	final= 78.0	se=1.6	-0.9 ^B	-5.7, 3.9	0.71							
					placebo	72		78	final= 78.9	se=1.8										
		SBP			Vit D ₃ 1000 IU/day	68		124.7	final= 122.5	se=2.0	-2.4 ^B	-8.6, 3.8	0.45							
					Vit D ₃ 2000 IU/day	73		122.8	final= 120.0	se=2.4	-4.9 ^B	-11.6, 1.8	0.15							
					Vit D ₃ 4000 IU/day	70		130.4	final= 126.6	se=2.6	+1.7 ^B	-5.3, 8.7	0.63							
					placebo	72		122.2	final= 124.9	se=2.4										
					Gepner 2012 ²²⁹ Madison, WI	Post- menopause		brachial DBP	2°	4 months	placebo	57	mmHg		72.6	change= -0.4	sd=4.4			A
								brachial DBP			Vit D ₃ 2500 IU/day	57			72.45	change= -0.7	sd=5.1	-0.3	-2.1, 1.5	
brachial SBP	placebo	57	122.2	change= -2.5			sd=10.9													
brachial SBP	Vit D ₃ 2500 IU/day	57	122.3	change= -0.3			sd=8.4	+2.2			-1.4, 5.8	0.23								
central DBP	placebo	57	73.7	change= -0.5			sd=4.4													
central DBP	Vit D ₃ 2500 IU/day	57	73.5	change= -0.7			sd=5.1	-0.2			-2.0, 1.6	0.82								
central SBP	placebo	57	115.6	change= -2.1			sd=9.7													
central SBP	Vit D ₃ 2500 IU/day	57	116.7	change= -0.3			sd=7.0	+1.8			-1.3, 4.9	0.26								

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

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Jorde 2010 ²³⁰ Norway	19–50, 51–70 yrs	DBP	1°	1 yr	DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	114	mmHg	76.5	change=1.0	sd=7.4	+0.8	-1.3, 2.9	0.45	B
		DBP			(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day PP	104		74.9	change=1.0	sd=8.3	+0.8	-1.4, 3.0	0.48	
		DBP				112		74.8	change=0.2	sd=8.3				
		SBP				114		124	change=1.2	sd=11.4	+2.3	-0.9, 5.5	0.15	
		SBP				104		121	change=3.5	sd=11.8	+4.6	1.3, 7.9	<0.001	
		SBP				112		125	change= -1.1	sd=12.8				
Wood 2012 ²³¹ Aberdeen, UK	Post- menopause	DBP	1°	1 yr	400 IU Vit D/day	97	mmHg	77.68	change= -2.5	-3.6, -1.4	-0.4	-1.9, 1.1	0.60	A
		DBP			placebo	100		77.7	change= -2.1	-3.1, -1.0				
		SBP			400 IU Vit D/day	96		128.16	change= -2.2	-3.3, -0.7	+0.2	-2.2, 2.6	0.87	
		SBP			placebo	98		128.18	change= -2.4	-4.5, -0.2				

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

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu 2013 ²³² Shanghai, China	19–50 yrs	DBP	1°	12 weeks	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22	mmHg	70.7	final=64.2	sd=4.7	-1.2	-4.6, 2.2	0.48	B
		DBP			energy-restricted diet alone (control)	21		70	final=65.4	sd=6.3				
		SBP			(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22		119.2	final=109.6	sd=9.9	-2.3	-8.6, 4.0	0.46	
		SBP			energy-restricted diet alone (control)	21		123	final=111.9	sd=10.4				
Daly 2009 ²³³ Melbourne, Australia	51–70 yrs	DBP	1°	2 yrs	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day	66	mmHg	69.5	change=4.2	2.1, 6.2	+0.3	-2.6, 3.2	0.84	A
		DBP			control (no additional fortified milk)	58		71	change=3.9	2.0, 5.8				
		SBP			(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day	66		123.7	change=6.8	4.2, 9.3	+1.5	-2.4, 5.4	0.45	
		SBP			control (no additional fortified milk)	58		120.4	change=5.3	2.4, 8.2				

Note: Outcomes cells are shaded for the Control rows.

^AEstimated from available data; ^B Estimated net difference and p-value from data

Vitamin D and Bone Mineral Density or Bone Mineral Content

The current report identified a number of RCTs that examined the effect of supplementation with vitamin D alone or vitamin D plus calcium on bone mineral density(BMD)/content (BMC), falls, and muscle strength and met criteria for inclusion. Studies that report on supplementation with vitamin D plus calcium (compared with a placebo) are described later in the report.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), **the original report** relied on a recent comprehensive systematic review performed by the Ottawa EPC (Table 28).⁸ 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, only bone mineral density (BMD) indices were included. For children, only bone mineral content (BMC) indices were included. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

Eight studies were identified for the current report that assessed the effects of supplemental vitamin D on bone mineral content or density. Of the seven studies, a study in infants and a study in postmenopausal women, showed a trend toward increasing BMC or BMD, respectively.

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.⁸ 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)

Current Report

Eight studies examined the effects of supplementation with vitamin D alone (or vitamin D plus calcium compared with calcium alone): one in infants,²³⁹ two in adolescent girls in India²⁴⁰ and Denmark and the remainder in adults.²⁴¹⁻²⁴⁵ Study duration ranged from 10 weeks (for the infants) to 2 years, with most lasting 1 year. Daily doses ranged from 200IU to 5700IU.

The study of infants (rated A), which administered doses ranging from 400IU to 1600IU daily from 2 weeks of age to 12 weeks of age observed a trend toward increasing BMC.²³⁹ One study of adolescents (rated B) showed slightly increased BMC in girls within 2 years of menarche. And a study of 305 postmenopausal Scottish women who received 0, 400, or

1000IU/d showed decreased loss of hip but not spine BMD with 1000IU/d.^{240,245} The remaining studies (one rated A, three B, one C) found no effects of vitamin D supplementation on BMD.

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 (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 D₃ 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 D₂ supplementation on hip BMC in 256 elderly women between 70 and 90 years of age. All elderly women in this trial had normal physical functioning. They were randomly assigned to receive either vitamin D₂ (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 D₂ plus calcium and calcium alone groups (hip BMD change: vitamin D, +0.5%; control, +0.2%).

One B quality RCT analyzed 89 and 83 healthy adult women and men separately.²⁴⁶ 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 D₃, 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 D₃ (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.^{48,246} The first RCT analyzed 26 healthy girls, who were Pakistani immigrants primarily living in the Copenhagen area Denmark (latitude 55 N°).²⁴⁶ Girls were randomly assigned to receive either daily dose 400 IU or 800 IU vitamin D₃, 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 D₃ (400 IU/d or 800 IU/d) and the placebo groups. The second RCT analyzed 168 healthy girls, living in the Greater Beirut area, Lebanon (latitude 33°N).⁴⁸ Girls were randomly assigned to receive either weekly oral vitamin D doses of 1400 IU (equivalent to 200 IU/d) or 14,000 IU (equivalent to 2000 IU/d) or placebo for one year. The mean baseline dietary calcium intake was 677 mg/d and mean 25(OH)D concentration was 35 nmol/L. At the end of study, there were no significant differences in whole body BMC changes between either low-dose vitamin D (200 IU/d) or high-dose vitamin D (2000 IU/d) and the placebo groups. The same findings were seen when analyses were restricted to either premenarchal or postmenarchal girls. Both RCTs were rated C because the results were not adjusted for important potential confounders, such as height, bone area, lean mass, sun exposure, and pubertal status.

Findings by Life Stage

- **0–6 mo**

One study identified for the current report found a trend toward increasing BMC for infants given high-dose supplements of vitamin D. 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**
Two RCTs identified for the current report assessed the effects of vitamin D supplementation on BMC in adolescent girls: One, which administered high doses, observed a trend for girls within two years of menarche. The other saw no effects.
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**
RCTs identified for the current report for populations of adults observed no effects of vitamin D on BMD. 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 D₃ (400 IU/d or 800 IU/d) and the placebo groups.
- **51–70 y**
RCTs identified for the current report for populations of adults observed no effects of vitamin D on BMD. 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 D₃ (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 D₂ supplementation (1000 IU/d) had no additional effect on hip BMD compared to calcium supplementation alone.

- **Postmenopause**

Two RCTs of vitamin D supplementation of postmenopausal women identified for the current report found no effect. One RCT found an effect on hip BMD but not spinal BMD and only at the higher of two doses (1000IU vs. 400IU/d). There were no new data since the Ottawa report.

- **Pregnant & lactating women**

No studies identified for the current report enrolled this population. 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 (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Zhu 2008 ²⁴⁷ Perth, Australia (32 °S) [18410225]	<ul style="list-style-type: none"> • 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 ²⁴⁶ Copenhagen, Denmark (55 N°) [18208636]	<ul style="list-style-type: none"> • 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 ⁴⁸ Beirut, Lebanon (33°53'N) [16278262]	<ul style="list-style-type: none"> • 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 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies					
Grimnes 2012 ²⁴¹ Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Post-menopausal 63.5 (SD 6.8) 0%	Serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L	high dose (6500 IU/day)+1000 mg elemental calcium/day vs. standard dose(800 IU/day)+1000 mg elemental calcium/day	97% compliance
Holmlund-Suila 2012 ²³⁹ Helsinki, Finland	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd Birth 50%	53 nmol/L	Vit D ₃ 1600 IU/day Vs. Vit D ₃ 1200 IU/day Vs. Vit D ₃ 400 IU/day	82% compliance
Iuliano-Burns 2012 ²⁴² Australian Antarctic Division	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 41 (24–65) 83%	Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose- 63+/-12 nmol/L	monthly (Vit D ₃ 50,000 IU/month) vs. bimonthly (Vit D ₃ 50,000 IU in alternate months) vs. single dose (one does of Vit D ₃ 50,000 IU pre departure)	
Jorde 2010 ²⁴³ nd	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight/Obese 50.8 (10.7) nd	57.7 +/-20.7 nmol/L	DD (Vit D ₃ 40,000 IU/week+500 mg calcium Vs.) DP (Vit D ₃ 20,000 IU/week+500 mg calcium) Vs. PP (Placebo+500 mg calcium)	Vitamin D- DD-95%, DP-96%, PP-96%, calcium-82%, 84%, and 83%
Khadiolkar 2010 ²⁴⁰ Pune, India	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd 14.6 (14.3–15.3) 0%	Vit D + Ca- 24.5 nmol/L (12.7–33.2) Placebo +Ca- 20.8 nmol/L (12.7–30.4)	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day Vs. Placebo x 4 times/year + 250 mg elemental calcium/day	nd

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Molgaard 2010 ²⁴⁸ Copenhagen and Frederiksberg, Denmark	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 11.4 (SD 0.2) 0%	Vitamin D intake: placebo- 2.6±1.4ug/d Serum vitamin D level:placebo- 43.4±17.1 nmol/L Calcium intake: placebo- 955±588 mg/d	10 µg Vit D ₃ /day Vs. 5 µg Vit D ₃ /day Vs. placebo	placebo:88±12 5ug/d: 90±10 10ug/d 88±11
Nieves 2012 ²⁴⁴ New York, US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Vit D deficient/depleted 61.2 (SD 7.6) 0%	Serum 25(OH)D: 29.0±14.3 nmol/L	1,000 IU Vit D ₃ Vs. placebo	95%
Macdonald 2013 ²⁴⁵ Scotland, UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, post menopausal 64.6 (SD 2.3) 0%	35.8±16.4 nmol/L	Vit d3 400 IU Vs. Vit d3 1000 IU Vs. placebo	92% (range 72% to 98%)

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

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu 2008 ²⁴⁷ 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	0.50%	-0.09, 1.09	0.30%	nd	NS	A
					Ca citrate 1200 mg	133		826	0.20%	-0.19, 0.59				
Andersen 2008 ²⁴⁶ 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 ²⁴⁶ 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 ²⁴⁶ 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	7-Sep		1.5	10%	nd	-5%	nd	NS	
					Placebo	7-Aug		1.7	15%	nd				
El-Hajj 2006 ⁴⁸ Beirut, Lebanon (33°N) [16278262]	10–17 y girls	BMC	1°	12	Vit D 2000 IU	55	kg	1.2	6.20%	4.7, 7.7	0.10%	-1.1, 2.0 ^C	NS	C
					Vit D 200 IU	58		1.1	6.10%	4.6, 7.6	1.10%	-0.8, 3.2 ^C	NS	
					Placebo	55		1.1	5.00%	3.8, 6.2				
	Subgroup– Pre- menarchal girls, mean age 10 y	BMC	1°	12	Vit D 2000 IU	14	kg	0.8	11.60%	9.4, 13.8	4.20%	0.7, 7.7 ^C	NS	
					Vit D 200 IU	12		0.7	11.40%	9.1, 13.7	4.00%	0.5, 7.5 ^C	NS	
					Placebo	8		0.8	7.40%	4.7, 10.1				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality				
NEW Studies																		
Grimnes 2012 ²⁴¹ Norway	Postmeno- pause	Total hip BMD	1°	1 yr	high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.79	change=0 .31	sd=1.59	-0.25	-0.63, 0.13	0.19	A				
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.791	change=0 .56	sd=1.70								
		Femoral neck BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.758	change=0 .03	sd=2.08	-0.14	-0.59, 0.31	0.86					
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.757	change=0 .17	sd=1.87								
		L2-L4 BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.901	change=0 .25	sd=3.19	-0.07	-0.80, 0.66	0.85					
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.902	change=0 .32	sd=3.23								
	Total Body BMD	high dose (6500 IU/day)+1000 mg elemental calcium/day			149	g/cm ²	1	change=0 .18	sd=1.14	-0.02	-0.29, 0.25	0.88						
		standard dose(800 IU/day)+1000 mg elemental calcium/day			148	g/cm ²	1.002	change=0 .20	sd=1.23									
	Holmlund-Suila 2012 ²³⁹ Helsinki, Finland	0–6 mos			cortical bone density	2°	10 week (age of 3 months)	Vit D ₃ 1600 IU/day	29	g/cm ³	NR	final=716	se=7		-8	-12.1, -3.9	<0.001	A
								Vit D ₃ 1200 IU/day	28		NR	final=726	se=7		+2	-2.1, 6.1	0.34	
total and trabecular bone density			Vit D ₃ 400 IU/day	25				NR	final=724	se=8								
			Vit D ₃ 1600 IU/day	29				NR	final=430	se=12	-18	-25, -11	<0.001					
			Vit D ₃ 1200 IU/day	28				NR	final=451	se=12	+3	-4, 10	0.39					
			Vit D ₃ 400 IU/day	25				NR	final=448	se=13								

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Iuliano-Burns 2012 ²⁴²	19–50, 0– 70 yrs	Femoral neck BMD	1°	up to 12 months (end of expedition)	monthly (Vit D ₃ 50,000 IU/month)	36	g/cm ²	0.86	final= 0.85	sd=0.13	-0.06	-0.12, 0	0.06	B
Australian Antarctic Division					bimonthly (Vit D ₃ 50,000 IU in alternate months)	35		0.82	final= 0.82	sd=0.10	-0.09	-0.15, -0.03	<0.001	
					single dose (one dose of Vit D ₃ 50,000 IU pre departure)	31		0.9	final= 0.91	sd=0.13				
		Lumbar spine (L1- L4) BMD			monthly (Vit D ₃ 50,000 IU/month)	36	1	final= 0.98	sd=0.16	-0.09	-0.17, -0.01	0.03		
					bimonthly (Vit D ₃ 50,000 IU in alternate months)	35	1	final= 1.00	sd=0.09	-0.07	-0.14, -0.0	0.05		
					single dose (one dose of Vit D ₃ 50,000 IU pre departure)	31	1.08	final= 1.07	sd=0.18					
		Total proximal femur BMD			monthly (Vit D ₃ 50,000 IU/month)	36	1.02	final= 0.85	sd=0.13	-0.23	-0.30, -0.16	<0.001		
					bimonthly (Vit D ₃ 50,000 IU in alternate months)	35	1.01	final= 1.01	sd=0.08	-0.07	-0.13, -0.01	0.02		
					single dose (one dose of Vit D ₃ 50,000 IU pre departure)	31	1.08	final= 1.08	sd=0.15					

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Jorde 2010 ²⁴³ nd	19–50, 51– 70 yrs	BMD L2-L4	1°	1 yr	DD (Vit D ₃ 40,000 IU/week+500 mg calcium)	110	g/cm ²	1.27	change=0 .008	sd=0.036	+0.00	-0.01, 0.01	0.85	B
					DP (Vit D ₃ 20,000 IU/week+500 mg calcium)	97		1.235	change=0 .008	sd=0.039	+0.01	0.0, 0.01	0.86	
					PP (Placebo+500 mg calcium)	105		1.251	change=0 .007	sd=0.042				
		BMD total hip			DD (Vit D ₃ 40,000 IU/week+500 mg calcium)	110		1.107	change=0 .008	sd=0.014	-0.00	-0.01, 0.0	0.64	
					DP (Vit D ₃ 20,000 IU/week+500 mg calcium)	97		1.067	change=0 .011	sd=0.014	+0.0	-0.0, 0.01	0.36	
					PP (Placebo+500 mg calcium)	105		1.092	change=0 .009	sd=0.017				
Khadilkar 2010 ²⁴⁰ Pune, India	9–18 yrs	L2-L4 bone mineral apparent density	1°	1 yr	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g/cm ³	NR	change=4 .2	0.6, 9.3	+0.5	NC	NC	B
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g/cm ³	NR	change=3 .7	1.0, 7.7				
	L2-L4 BMC	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day			25	g	NR	change=1 0.5	4.6, 17.2	-0.8	NC	NC		
		Placebo x 4 times/year + 250 mg elemental calcium/day			24	g	NR	change=1 1.3	5.4, 18.0					
	Total BMC	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day			25	g	NR	change=1 0.1	6.1, 14.7	+1.9	NC	NC		
		Placebo x 4 times/year + 250 mg elemental calcium/day			24	g	NR	change=8 .2	4.9, 12.6					

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality		
Molgaard 2010 ²⁴⁸ Copenhagen and Frederiksberg, Denmark	9–18 yrs	L1-L4 BMC	1°	12 months	10 µg Vit D ₃ /day	74	g	28.9	final=36.3	sd=8.6	-1.2	-4.3, 1.9	0.44	B		
					5 µg Vit D ₃ /day	73	g	29.4	final=37.6	sd=10.3	+0.1	-3.2, 3.4	0.95			
					placebo	74	g	29.2	final=37.5	sd=10.2						
		L1-L4 BMD			10 µg Vit D ₃ /day	74	g/cm ²	0.695	final=0.78	sd=0.113	-0.01	-0.05, 0.03	0.68			
		5 µg Vit D ₃ /day			73	g/cm ²	0.698	final=0.78	sd=0.115	-0.0	-0.04, 0.04	0.91				
		placebo			74	g/cm ²	0.697	final=0.78	sd=0.121							
	whole body BMD	10 µg Vit D ₃ /day			74	g/cm ²	0.872	final=0.91	sd=0.080	+0.01	-0.02, 0.03	0.53				
		5 µg Vit D ₃ /day			73	g/cm ²	0.866	final=0.91	sd=0.075	+0.01	-0.02, 0.03	0.63				
		placebo			74	g/cm ²	0.863	final=0.90	sd=0.075							
		whole body BMC			10 µg Vit D ₃ /day	74	g	1308	final=1561	sd=366	+38	-74, 150	0.50			
		5 µg Vit D ₃ /day			73	g	1311	final=1559	sd=324	+36	-70, 142	0.50				
		placebo			74	g	1277	final=1523	sd=324							
Nieves 2012 ²⁴⁴ New York, US	Postmeno- pause	femoral neck BMD	1°	2 yrs	1,000 IU Vit D ₃	55	g/cm ²	NR	change=- 0.2	NR	+0.6	NC	NC	A		
					placebo	48		NR	change=- 0.8	NR						
		spine BMD			1,000 IU Vit D ₃	55		1.154	change=- 0.5	NR	+0.1	NC	NC			
					placebo	48		1.212	change=- 0.6	NR						
		total hip BMD			1,000 IU Vit D ₃	55		1.043	change=- 0.5	NR	+0.2	NC	NC			
					placebo	48		1.04	change=- 0.7	NR						
		trochanter BMD			1,000 IU Vit D ₃	55		NR	change=- 0.3	NR	+0.15	NC	NC			
					placebo	48		NR	change= -0.45	NR						

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base- line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Macdonald 2013 ²⁴⁵		total hip BMD	1°	1 yr	Vit d3 400 IU	83	g/cm2	0.917	final= 0.912	sd=0.103	-0.002	-0.036, 0.032	0.91	A
					Vit d3 1000 IU	88		0.923	final= 0.923	sd=0.135	+0.009	-0.029, 0.047	0.64	
					placebo	88		0.92	final= 0.914	sd=0.118				
		total lumbar spine BMD			Vit d3 400 IU	83		1.075	final= 1.076	sd=0.135	+0.006	-0.038, 0.050	0.79	
					Vit d3 1000 IU	88		1.068	final= 1.071	sd=0.164	+0.001	-0.046, 0.048	0.97	
					placebo	88		1.081	final= 1.070	sd=0.153				

Note: Outcomes cells are shaded for the Control rows.

^ABaseline/final sample size

^BDowngraded to C because very small sample size (insufficient power) and no adjustments for confounders

^CEstimated 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 D₃ 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 and Calcium and Growth

The current report did not consider growth as an outcome, except for prenatal growth. No new studies were identified. The original report reviewed primary studies that evaluated relationships between vitamin D and calcium 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

The original report 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.⁵⁴ 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% 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% 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% 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. **As described in the original report**, a variety of cardiovascular events after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined daily vitamin D₃ 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.

A reassessment of the WHI Ca-D Trial data that controlled for women's use of personal dietary supplements found no effects of the intervention vitamin D and calcium supplements on risk for cardiovascular outcomes.

Detailed Presentation (Tables 46 & 47)

The original report described the findings of the WHI CaD with respect to cardiovascular outcomes. In the WHI trial, discussed above, the evaluated cardiovascular outcomes were all prespecified secondary outcomes.^{249,250} 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% CI 0.99, 1.19]), coronary artery bypass grafting or percutaneous coronary interventions (HR=1.09 [95% CI 0.98, 1.22]), and transient ischemic attacks (HR=1.16 [95% 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.

A post hoc analysis of the WHI CaD Trial data was found for the current report that assessed the effects of the study intervention after controlling for women's use of personal dietary supplements. This analysis found no effects of the intervention vitamin D and calcium supplements on risk for cardiovascular outcomes among women who did not use Ca or vitamin D supplements at the start of the trial (rated A).²

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 D₃ (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 46. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs (formerly Table 85) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Hsia 2007 ²⁴⁹ LaCroix 2009 ²⁵⁰ WHI US (various) [17309935 19221190]	<ul style="list-style-type: none"> • 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 discussion of use of personal supplements in the WHI trial in “Colorectal Cancer, Detailed Presentation”
NEW Studies						
Prentice 2013 ² WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Post- menopausal 50–54: 14.2% (50-79) 0%	nd	1000mg/day of Ca & 400IU/day of Vit D3 Vs. placebo	nd	

Table 47. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs (formerly Table 86) (updated from original report)

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 ²⁴⁹ LaCroix 2009 ²⁵⁰ 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	0.1	
					Placebo	841	18,106					
		Cardiac composite (MI or CHD death)	2°		Vit D + Ca	499	18,176	HR	1.04	0.92, 1.18	0.5	
					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	0.5	
					Placebo	407	18,106					
		Angina	2°		Vit D + Ca	404	18,176	HR	1.08	0.94, 1.24	0.3	
					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					

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
New studies												
Prentice 2013 ² WHI US (various)		Primary - MI	1°	7	1000mg/day of Ca & 400IU/day of Vit D3	193	7,718	HR	1.18	0.88, 1.59	0.17	A
					placebo	167	7,584		1.00	Reference		
		Primary - Coronary heart disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	229	7,718	HR	1.08	0.82, 1.42	0.4	
					placebo	211	7,584		1.00	Reference		
		Primary - Total heart disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	621	7,718	HR	1.00	0.86, 1.18	0.56	
					placebo	642	7,584		1.00	Reference		
		Primary - Stroke	1°		1000mg/day of Ca & 400IU/day of Vit D3	184	7,718	HR	1.18	0.86, 1.62	0.96	
					placebo	162	7,584		1.00	Reference		
		Primary - Total cardiovascular disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	848	7,718	HR	1.04	0.90, 1.19	0.77	
					placebo	813	7,584		1.00	Reference		

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Body Weight

The current report did not consider the topic of body weight. The original report 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), **that report** 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 D₂ 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 48 & 49)

Isocaloric Diet

The WHI trial was analyzed for the effect of daily combined vitamin D₂ 400 IU and calcium carbonate 1000 mg on weight.²⁵¹ The trial included about 36,000 postmenopausal women aged 50 to 79 years. The methodological quality of the study was B. At 7 year follow up, the net change in body weight (supplemented minus control) was -0.13 kg (95% 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 D₂ 400 IU and calcium carbonate 1200 mg versus placebo.²⁵² 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 dropout 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 48. Combined vitamin D and calcium and weight: Characteristics of RCTs (formerly Table 87) (no new studies in the current report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Caan 2007 ²⁵¹ WHI US (various) [17502530]	<ul style="list-style-type: none"> • 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 discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	Factorial design with HT vs. Placebo
Major 2007 ²⁵² Quebec City, Canada (47°N) [17209177]	<ul style="list-style-type: none"> • 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 49. Combined vitamin D and calcium and weight: Results of RCTs (formerly Table 88) [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	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 ²⁵¹ 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 ²⁵² 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				

Note: Outcomes cells are shaded for the Control rows

^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

This section explores 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 D₃ and calcium supplementation on the risk of total cancer. The WHI showed no effects,¹³¹ while the trial conducted in Nebraska (latitude 41°N) reported significant reduction of risk of total cancer.¹⁰² 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 50 & 51)

The 7-year WHI trial that enrolled 36,282 postmenopausal women across the United States compared a daily supplement of vitamin D₃ (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.¹³¹ 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 D₃ and calcium supplementation on either the risk of total cancer (adjusted HR: 0.98, 95% CI 0.91, 1.05) or total cancer mortality (adjusted HR: 0.89, 95% CI 0.77, 1.03). The methodological quality of this study was rated B.

A 4-year population-based RCT¹⁰² sampled from a 9-county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D₃ (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 D₃ (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% CI 0.20, 0.82; P=0.013) for the vitamin D₃ 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 D₃ plus calcium group changed to 0.23 (95% 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 D₃ 400 IU/d plus calcium carbonate 1000 mg/d showed no effects, while the trial in Nebraska using vitamin D₃ 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 50. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs (formerly Table 89) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006 ¹³¹ WHI US (various) [16481636]	<ul style="list-style-type: none"> • 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 discussion of use of personal supplements in the WHI trial in “Colorectal Cancer, Detailed Presentation”
Lappe 2007 ¹⁰² Nebraska, US (41° N) [17556697]	<ul style="list-style-type: none"> • 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
NEW Studies					
Prentice 2013 ² WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y 	Post- menopausal women 50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%; (50–79)	nd	400 IU Vit D ₃ + 1,000 mg elemental calcium carbonate Vs. placebo	nd
Brunner 2011 ²⁵³ WHI nd	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y 	nd (50–79)	nd	1,000 mg elemental calcium + 400 IU of vitamin D ₃ Vs. placebo	nd

Table 51. Combined vitamin D and calcium and total cancer incidence: Results of RCTs (formerly Table 90) (updated from original report)

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 ¹³¹ 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 ¹⁰² [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	0.4	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					
NEW Studies												
Prentice 2013 ² WHI US (various)		Secondary - Total invasive cancer	1°	7.2 yrs	400 IU Vit D3 + 1,000 mg elemental calcium carbonate	553	7718	adjusted HR	0.88	0.78, 0.98	NR	A
					placebo	617	7584		1.00	Reference		
Brunner 2011 ²⁵³ WHI nd	Post- menopausal women	Total cancer	1°	7 yrs	1,000 mg elemental calcium + 400 IU of vitamin D3	1306	18176	adjusted HR	0.98	0.90, 1.05	0.78	A
					placebo	1333	18106		1.00	Reference		

Note: Outcomes cells are shaded for the Control rows.

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 D₃ and calcium and, colorectal cancer mortality or incidence.

Detailed Presentation (Tables 52 & 53)

The WHI CaD trial, **described in the original report**, compared daily supplemental vitamin D₃ (400 IU) and elemental calcium (1000 mg) with placebo in 36,282 postmenopausal women. Colorectal cancer was evaluated as a secondary endpoint.¹³¹ The primary endpoint was the prevention of hip fracture. At 7 years vitamin D₃ 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 personal calcium or vitamin D supplements; they had mean daily total calcium intake of 1151 mg and vitamin D intake of 367 IU at enrollment. **A post hoc analysis of the WHI CaD 7-year trial data identified for the current report compared the risk for colorectal cancer among participants who had not been taking personal calcium and vitamin D supplements at baseline with that of participants who had taken supplements; the hazard ratio for colorectal cancer risk among all participants was 1.30 (95% CI 0.88, 1.92), compared with 0.99 (95% CI 0.56, 1.77) for women who had taken no personal supplements.**²

Findings for 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.¹³¹ 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.²⁵⁴ 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% 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% 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 D₃ (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 52. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs (formerly Table 91) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006 ¹³¹ WHI US (various) [16481636]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%) 0	Total Ca intake (mg/d) (Mean for both groups: 1151) Ca + Vit D arm: 1148 <ul style="list-style-type: none">• <800: 34%• 800-<1200: 26%• ≥1200: 39% Placebo arm: 1154 <ul style="list-style-type: none">• <800: 33%• 800-<1200: 26%• ≥1200: 40% Total Vit D intake (IU/d) (Mean for both groups: 367) Ca + Vit D arm: nd <ul style="list-style-type: none">• <200: 38%• 200-<400: 19%• 400-<600: 23%• 600: 19% Placebo arm: nd <ul style="list-style-type: none">• <200: 37%• 200-<400: 19%• 400-<600: 24%• 600: 19%	Ca 1000 mg/d + Vit D ₃ 400 IU/d vs. Placebo	See discussion of use of personal supplements in the WHI trial in “Colorectal Cancer, Detailed Presentation”	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 follow up: <ul style="list-style-type: none">• Ca + Vit D arm: 0.8%• Placebo arm: 0.8% Withdrawn: <ul style="list-style-type: none">• Ca + Vit D arm: 1.9%• Placebo arm: 1.8%

Table 53. Combined vitamin D with calcium and colorectal cancer: Results of RCTs (formerly Table 92) [no new studies in the current report]

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 ¹³¹ 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			Vit D + Ca	168	18,176	HR	1.08	0.86, 1.34	0.51	
					Placebo	154	18,106					
		Colon cancer			Vit D + Ca	128	18,176	HR	1.00	0.78, 1.28	0.99	
					Placebo	126	18,106					
		Rectal cancer			Vit D + Ca	44	18,176	HR	1.46	0.92, 2.32	0.11	
					Placebo	30	18,106					

Note: Outcomes cells are shaded for the Control rows.

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 D₃ 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 (Tables 52 & 53)

The WHI compared a daily supplement of vitamin D₃ (400 IU) and elemental calcium (1000 mg) with placebo and evaluated incidence of self-reported colorectal adenoma as part of multiple secondary analyses.¹³¹ 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.²⁵⁵ 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% CI 0.57,0.89] versus HR=1.05 [95% 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 D₃ 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 WHI CaD trial versus placebo in 50 to 79 year old women without a prior history of breast cancer, **identified for the original report.**²⁵⁶ 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 54 & 55)

In the WHI trial, the evaluated breast cancer incidence and breast cancer related mortality outcomes were secondary outcomes.²⁵⁶ 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. **A post hoc analysis of the WHI CaD 7-year trial data identified for the current report compared the risk for breast cancer among participants who had not been taking personal calcium and vitamin D supplements at baseline with that of participants who had 0.89 (95% CI 0.72, 1.11), compared with 0.73 (95% CI 0.52, 1.02) for women who had taken no personal supplements, suggesting a trend toward decreased risk for breast cancer among those who did not use supplements at baseline.**²

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 D₃ (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 54. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs (formerly Table 93) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Chlebowski 2008 ²⁵⁶ WHI US (various) [19001601]	<ul style="list-style-type: none"> • 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 55. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs (formerly Table 94) [no new studies in the current report]

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
Chlebowski 2008 ²⁵⁶ 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					

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Pregnancy-Related Outcomes

Preeclampsia

Synopsis

Based on data from a single RCT **identified for the original report**, there is no significant effect of combined vitamin D and calcium supplementation on the prevention of preeclampsia.

Detailed Presentation (Tables 56 & 57)

One RCT from India used a combination of vitamin D (1200 IU/d) and calcium (375 mg/d) for the prevention of preeclampsia.²⁵⁷ **Table 56** describes the characteristics of the trial. The trial found no significant difference between the compared arms (**Table 57**).

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 calcium and high blood pressure, preterm birth, or small for gestational age infant.

Table 56. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs (formerly Table 95) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Marya 1987 ²⁵⁷ India (29°N) [3623260]	<ul style="list-style-type: none"> • 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 57. Combined vitamin D and calcium and preeclampsia: Results of RCTs (formerly Table 96) [no new studies in the current report]

Author Year Study Name Location (Latitude) [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
Marya 1987 ²⁵⁷ 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					

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health

Rickets, Fractures, Falls, or Performance Measures

For the current report, we identified no new studies on the effect of vitamin D and calcium supplementation on rickets that met the inclusion criteria; we identified two RCTs that assessed the effect of vitamin D and calcium supplementation on fracture risk (described in Table 59 and the accompanying text), one RCT that assessed effects on muscle strength (Table 60), and one that assessed effects on risk for falling (Table 60) (studies that assessed the effects of supplementation with vitamin D and calcium on bone mineral density or bone mineral content are described in Table 66 and the accompanying text).

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), the **original report** relied on a recent comprehensive systematic review performed by the Ottawa EPC (Table 34).⁸ 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 current report identified two RCTs that found no effect of an intervention with vitamin D and calcium on osteoporotic fracture risk among postmenopausal women, one RCT of vitamin D and calcium that found no effect on muscle strength in middle-age and older men, and one RCT that found no effect on risk for falls among older women.

The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D₃) plus calcium is effective in reducing fractures in institutionalized populations, but 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 **and included in the original 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 follow up.²⁵⁸ 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.²⁵⁹

Detailed Presentation (Tables 34, 58, 59, & 60)

The current report identified two RCTs of vitamin D and calcium that assessed osteoporotic fracture risk. One, a re-analysis of data from the WHI CaD trial that attempted to assess the effects of the intervention alone (separate from use of additional personal supplements), found no significant effect of the intervention on overall fracture risk at 6 years (rated B).² The second RCT, the OSTPRE study, also found no effect of 3

years' supplementation with calcium and vitamin D on risk for total, nonvertebral, distal forearm, upper extremity, or lower extremity fragility fractures among 3,195 postmenopausal women, 65 to 71 years of age (rated B).²⁶⁰

One RCT on middle-age and older Australian men (age 50 to 79) tested the effect of an 18-month intervention of daily vitamin D (800IU) and calcium (1000mg) on measures of muscle function (rated A). No effect was seen on any measure of muscle function, including step test, gait speed or sway.²⁶¹

An RCT that tested the effect of a 3-year intervention of daily vitamin D (800IU) and calcium (1000mg) on risk for falls among 812 older Finnish women (mean age 67) found no effect on fall risk (study rated C).²⁶²

In the original report, 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).²⁵⁹ 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.²⁵⁸ 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 D₂ or D₃ 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 D₃. There were no trials identified in premenopausal women.

Meta-analysis results from 13 RCTs of vitamin D₂ or D₃ 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 D₃. When combining seven RCTs of vitamin D₃ (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 D₃), 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 D₂ or D₃ (oral or injectable) with or without calcium (OR 0.89, 95% CI 0.80, 0.99). The individual treatment effects ranged from OR 0.28 (95% CI 0.12, 0.67) to 1.16

(95% 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 D₃ plus calcium (RR 0.88, 95% 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 D₂ (RR 1.09, 95% CI 0.95, 1.25). Meta-analysis of eight RCTs of oral vitamin D₂/D₃ supplementation with calcium showed a reduction in the risk of falls, whereas four RCTs of oral vitamin D₃ 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 follow up 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 D₃) 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**
One RCT identified for the current report found no differences in any measure of muscle strength between men (50 to 70) who received supplemental vitamin D and calcium for 18 months and those who received placebos. No new data were identified for the original report since the Ottawa report
- **71+**
No new data since the Ottawa report
- **Postmenopause**
Two studies identified for the current report (one a reanalysis of data from the WHI study) found no differences in fracture risk between women supplemented with vitamin D and calcium and placebo groups (3 to 6 years). 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 follow up.
- **Pregnant & lactating women**
No data

Table 58. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 97) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2008 ²⁵⁹ Great Lakes, IL, US (41°N) [18433305]	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Assumed healthy (Navy recruits) 19 (17–35)	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 ²⁵⁸ WHI US (various) [18755319]	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd (for the sub sample from WHI trial) 50–79	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)
NEW Studies					
Prentice 2013 ² WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Post-menopausal 50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%; (50–79)	nd	400 IU Vit D3 + 1,000 mg elemental calcium carbonate Vs. placebo	nd
Salovaara 2010 ²⁶⁰ OSTPRE Study nd	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 67.3 (SD 1.8)	Serum vitamin D: 49.1±17.7 nmol/L	400 IU cholecalciferol + 500 mg calcium carbonate Vs. control (no intervention or placebo)	nd
Karkkainen 2010 ²⁶² OSTPRE-FPS Kuopio, Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 67.4 (SD 1.9) Range: 65–71	Intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (P = 0.544)	1g/daily & 800 IU/daily Vs. Placebo	78% compliance
Kukuljan 2009 ²⁶¹ Victoria, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 59.9 (SD 7.4) Range: 50–79	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.

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original 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
Lappe 2008 ²⁵⁹ [18433305]	17–35 y women	Stress fracture from Navy training (ITT)	1°	2 mo	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 mo	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					
NEW Studies												
Prentice 2013 ² WHI US (various)		Total fractures	1°	7.2 yrs	400 IU Vit D3 + 1,000 mg elemental calcium carbonate	872	7718	HR	0.97	0.88, 1.07	NR	A
					placebo	870	7584		1.00	Reference		
		Hip fracture			1000mg/day of Ca & 400IU/day of Vit D3	68	7718	HR	0.86	0.62, 1.20	NR	
					Placebo	80	7584		1.00	Reference		

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report) (continued)

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
Salovaara 2010 ²⁶⁰												
OSTPRE Study nd		any fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	78	1586	HR	0.83	0.61, 1.12		A
					control (no intervention or placebo)	94	1609		1.00	Reference		
		any nonvertebral fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	71	1586	HR	0.87	0.63, 1.19		
					control (no intervention or placebo)	82	1609		1.00	Reference		
		any osteoporotic fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	42	1586	HR	0.81	0.54, 1.22		
					control (no intervention or placebo)	52	1609		1.00	Reference		
		distal forearm fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	23	1586	HR	0.70	0.41, 1.20		
					control (no intervention or placebo)	32	1609		1.00	Reference		
		proximal humerus fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	6	1586	HR	1.01	0.32, 3.14		
					control (no intervention or placebo)	6	1609		1.00	Reference		
		hip fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	4	1586	HR	2.23	0.41, 12.29		
					control (no intervention or placebo)	2	1609		1.00	Reference		
		vertebral fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	9	1586	HR	0.67	0.29, 1.58		
					control (no intervention or placebo)	13	1609		1.00	Reference		
		upper extremity fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	41	1586	HR	0.75	0.49, 1.16		
					control (no intervention or placebo)	50	1609		1.00	Reference		
		lower extremity fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	22	1586		1.02	0.58, 1.80		
					control (no intervention or placebo)	20	1609		1.00	Reference		

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report) (continued)

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
Karkkainen 2010 ²⁶² OSTPRE-FPS Kuopio, Finland		Primary—No falls	1°	3 y	1g/daily & 800 IU/daily	754	1566	OR	1.05	0.91, 1.20	>0.05	C
					Placebo	740	1573	OR	1.00	Reference		
		Primary—Falls (≤1)			1g/daily & 800 IU/daily	1109	1566	OR	1.13	0.97, 1.32	>0.05	
					Placebo	1073	1573	OR	1.00	Reference		
		Primary—No fall requiring medical attention (FRMA)			1g/daily & 800 IU/daily	1308	1566	OR	0.84	0.70, 1.01	>0.05	
					Placebo	1274	1573	OR	1.00	Reference		
		Primary—Falls requiring medical attention (FRMA) (≤1)			1g/daily & 800 IU/daily	1488	1566	OR	0.72	0.53, 0.97	0.03	
					Placebo	1466	1573	OR	1.00	Reference		

Note: Outcomes cells are shaded for the Control rows.

Table 60. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures) (formerly Table 99) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1/2°	Mean Followup , mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseli ne	Change	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Brunner 2008 ²⁵⁸ [18755319]	Postmen opause	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	0.03	
					Placebo	1141			0.81	6.43				
NEW Studies														
Kukuljan 2009 ²⁶¹ Victoria, Australia	51–70 yrs	Step test	1°	18 mos	Ig & 800 IU daily	43	unit number	9.90	final= 11.4	SD=3.00	-6	-2.0, 0.75	0.38	A
					Control	42	unit number	10.30	final= 12.0	SD=3.30	reference			
		Gait speed			Ig & 800 IU daily	43	m/s	2.84	final= 2.79	SD=1.17	+0.13	-0.36, 0.62	0.60	
					Control	42	m/s	3.08	final= 2.66	SD=1.12	reference			
		Sway, eyes open, on floor			Ig & 800 IU daily	43	mm2	294.0	final=326	SD=344	+147	32.4, 261.6	0.01	
					Control	42	mm2	320.0	final=179	SD=147	reference			
		Sway, eyes closed, on floor			Ig & 800 IU daily	43	mm2	364.0	final=241	SD=192	-79	-207, 49	0.22	
					Control	42	mm2	285.0	final=320	SD=373	reference			
		Sway, eyes open, on foam			Ig & 800 IU daily	43	mm2	737.0	final=596	SD=733	+248	9, 487	0.04	
					Control	42	mm2	597.0	final=348	SD=266	reference			
		Sway, eyes closed, on foam			Ig & 800 IU daily	43	mm2	1317.0 0	final= 1045	SD=787	-209	-721, 303	0.42	
					Control	42	mm2	1437.0 0	final= 1254	SD=1489	reference			

Note: Outcomes cells are shaded for the Control rows.

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. **No new studies were identified for this outcome.** 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% 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% 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 11)

As mentioned in the Methods section, **the original report** updated and reanalyzed published meta-analyses of mortality outcomes. **The authors of that report** drew conclusions based on **their own** analyses **and** also comment on the concordance of **these** 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, **the original report** identified two potentially eligible systematic reviews,^{204,205} and selected one as the basis for our reanalysis (Autier 2007).²⁰⁴ Table 37 in the “Vitamin D” section summarizes the findings of the Autier 2007 systematic review.

As detailed below, **the original report** identified one additional trial of combined vitamin D and calcium supplementation reporting all-cause mortality.²⁶³

Eligible Studies Published After the Systematic Reviews

The literature searches in Autier 2007 extended up to November 2006. Two additional RCT reports **were identified for the original report** published after November 2006.^{131,263} One publication¹³¹ reported on the same trial as another publication²⁶⁴ in the Autier 2007 meta-analysis, and was therefore excluded from our reanalysis. The other RCT (Bjorkman 2008)²⁶³ was included in our meta-analysis.

One three-arm RCT (Bjorkman 2008)²⁶³, n=218) compared no supplementation versus daily supplementation with 400 IU and 1200 IU of vitamin D₃ 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

The re-analysis conducted for the original report excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,²⁰⁶ one was published only in abstract form,²⁰⁷ and in the last trial the controls also received supplementation with vitamin D, albeit with a smaller dose,²⁰⁸ and two used injections of vitamin D.^{209,210} 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 one²⁶³).

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 11 [formerly 22]) found no statistically significant relationship between vitamin D and all-cause mortality (RR=0.93, 95% CI 0.86, 1.01). There is little evidence for between-study heterogeneity in these analyses ($P=0.58$, $I^2=0\%$). Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95% CI 0.86, 1.00), again with little evidence for between-study heterogeneity ($P=0.46$, $I^2=0\%$). 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% CI 0.84, 1.15), with little evidence for between study heterogeneity ($P=0.33$, $I^2=13\%$).

Findings by Life Stage

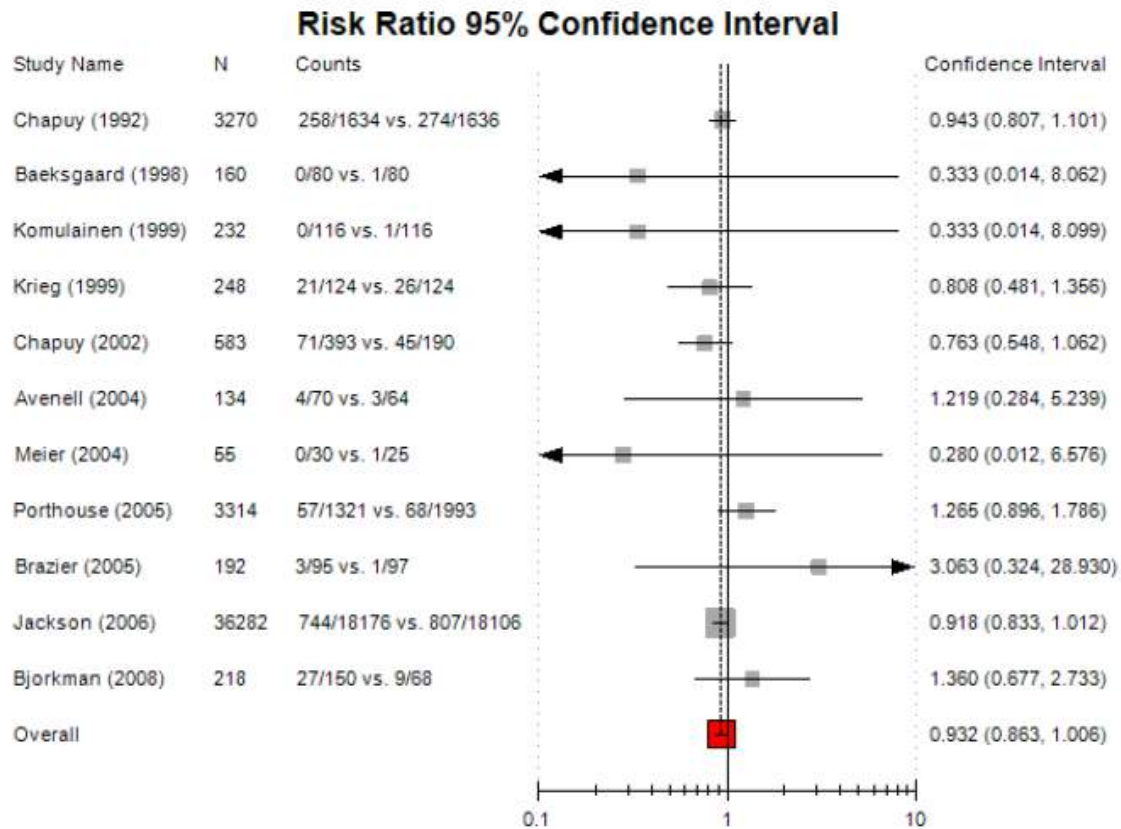
- **0–6 mo**
No data
- **7 mo–2 y**
No data
- **3–8 y**
No data
- **9–18 y**
No data
- **19–50 y**
No data
- **51–70 y**

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% 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% 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% CI 0.86, 1.00), again with little evidence for between-study heterogeneity.
- **Pregnant & lactating women**
No data

Figure 11. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality (formerly Figure 22)



Combined Vitamin D and Calcium and Hypertension and Blood Pressure

For the current report, we identified no new studies that addressed these outcomes. The original report 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 new studies were identified for this outcome. No systematic reviews that met our inclusion criteria 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 61 & 62)

The WHI trial of a combined vitamin D₃ 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).²⁶⁵ 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*). 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% 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 61. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008 ²⁶⁵ WHI US (various) [18824662]	<ul style="list-style-type: none"> • 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 62. Combined vitamin D and calcium and incident hypertension: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage [Subgroup]	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 ²⁶⁵ 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					
					Vit D + Ca	53			1.52	0.89, 2.59	NS	
					Placebo	38						
					Vit D + Ca	39			1.48	0.89, 2.46	NS	
					Placebo	48						
					Vit D + Ca	45			1.15	0.69, 1.92	NS	
					Placebo	45						
	[25(OH)D <34.4 nmol/L]				Vit D + Ca	48			0.79	0.51, 1.22	NS	
					Placebo	61						

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Blood Pressure

Synopsis

No new studies were identified that addressed this outcome. No systematic reviews that met our inclusion criteria 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 D₃ 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 63 & 64)

The WHI trial of a combined vitamin D₃ 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).²⁶⁵ 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 years²⁴⁹). 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).²⁵² The mean baseline calcium intake was 704 mg/day. On average, the 63 women had normal blood pressure. They were given either combined vitamin D₃ 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 D₃ 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 63. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs (formerly Table 102) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008 ²⁶⁵ WHI US (various) [18824662]	<ul style="list-style-type: none"> • 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 \geq 1200 mg/d	Combined Vit D + Ca supplement vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"
Major 2007 ²⁵² Quebec City, Canada (47°N) [17209177]	<ul style="list-style-type: none"> • 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 64. Combined vitamin D and calcium and blood pressure: Results of RCTs (formerly Table 103) [no new studies in the current report]

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 ²⁶⁵ 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 ²⁵² 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 ²⁶⁵ 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 ²⁵² 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				

Note: Outcomes cells are shaded for the Control rows.

^A Hsia 2007²⁴⁹ [17309935]

Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content

For the current report, we identified seven studies of the effect of combined calcium and vitamin D supplementation on bone mineral density or content (Table 66). For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), the original report relied on a recent comprehensive systematic review performed by the Ottawa EPC (Table 34).⁸ 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, only BMD indices were included. For children, only BMC indices were included. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

Of the seven RCTs identified for this report on the effect of vitamin D and calcium supplementation on bone density or content, six reported positive effects on BMD. Followup times ranged from 1 to 6 years. Vitamin D supplementation ranged from 200 to 800IU per day, with calcium ranging from 600 to 1200mg per day.

In the original study, one RCT found that, compared to placebo, there was no significant effect of supplementation with vitamin D₃ (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 D₃ (≤ 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.⁸ Two of the three new RCTs showed consistent findings in postmenopausal women, comparing vitamin D₃ or D₂ (300 or 1000 IU/d, respectively) plus calcium (1200 mg/d) to placebo.

Detailed Presentation (Tables 34, 65, & 66)

One RCT identified for the current study that randomized 10-year-old girls in China by school compared the effects of 560mg daily calcium and 200 to 320IU vitamin D-supplemented milk per day to habitual diet and found that total body BMD was significantly increased after 2 years.²⁶⁶

A 1-year intervention with vitamin D-depleted Indian women, 16 to 36 years of age, compared the effects of 400IU vitamin D and 600mg calcium per day to those of placebo and found significantly increased femoral neck but not lumbar spine BMD (study rated A).²⁶⁷

Four studies assessed the effect of vitamin D and calcium supplementation on postmenopausal women. A study conducted on a subgroup of 1,529 WHI participants on the ability of 400IU vitamin D and 1000mg calcium per day to preserve BMD found significant effects on specific areas such as the femoral narrow neck but only trends toward increased preservation of intertrochanteric and shaft BMD at year 6 (rated A).²⁶⁸ The OSTPRE-FPS trial of Finnish women, 65 to 71 years of age, found that 800IU vitamin D and 1,000 mg calcium daily significantly increased total body BMD but did not significantly increase femoral neck, lumbar spine or trochanteric BMD at 3 years (rated

C).²⁶⁹ The Postmenopausal Health Study randomized 66 women, 55 to 65 years, to 300IU vitamin D and 1200mg calcium or placebo daily for 12 months and then 900IU vitamin D plus 1200mg calcium for the next 18 months: Significant increases were achieved in total body and spinal BMD at 30 months (rated B).²⁷⁰ The Postmenopausal Health Study II randomized 65 women, 55 to 65 years, to 400IU vitamin D and 800mg calcium or control for 12 months: Significant increases were achieved in total body but not spinal BMD (rated B).²⁷¹

One RCT randomized 89 healthy, vitamin D-replete Australian men, 50 to 79 years of age, to milk fortified with 800IU vitamin D and 1000mg calcium per day or a control group; the fortified milk had no significant effects on BMD in any area in these men (rated A).²⁷²

One RCT identified for the original report compared the effect of vitamin D₃ (200 IU/d) plus calcium (1000 mg/d) supplementation to placebo on bone indices in healthy girls, aged 10 and 12 years.²⁷³ 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 D₃ plus 100 mg elemental calcium for 2 years.²⁷⁴ The second RCT used daily dose of 1000 IU vitamin D₂ plus 1200 mg calcium citrate for 5 years.²⁷⁵ The third RCT used a daily dose of vitamin D₃ 300 IU plus calcium citrate 1200 mg from calcium supplemented low-fat dairy products for 1 year.²⁷⁶ The latter two RCTs resulted in a significant increase in hip or total BMD comparing vitamin D plus calcium supplementation to placebo.^{275,276} 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 D₃ 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 D₃ supplementation alone has a significant effect on BMD.

Seventeen RCTs evaluated the effect of supplemental vitamin D₂ or D₃ 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 D₃ and also included calcium 500 mg as a cointervention.

Meta-analysis results of 17 RCTs of vitamin D₃ 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 D₃ plus 1000 mg calcium supplementation on total hip BMD. However, when the effect of vitamin D₃ plus calcium versus calcium alone supplementation is assessed, no significant increase in BMD was observed with either

intervention, suggesting vitamin D₃ may be of less benefit in calcium replete postmenopausal women. Vitamin D₃ 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 D₃ (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 D₃ (≤ 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 D₃ or D₂ (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 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Cheng 2005 ²⁷³ Jyväskylä, Finland (62°24'N) [16280447]	<ul style="list-style-type: none"> • 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 ²⁷⁴ (UK 54°N) [17243866]	<ul style="list-style-type: none"> • 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 ²⁷⁵ CIFOS Western Australia [18089701]	<ul style="list-style-type: none"> • 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 ²⁷⁶ Greece (31°N) [17181890]	<ul style="list-style-type: none"> • 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
NEW Studies					
Islam 2010 ²⁶⁷ Dhaka, Bangladesh	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) Healthy 22.9 (SD 3.9) 0%	placebo-35.0 +/- 9.4 nmol/L Vit D-37.1 +/- 12.1 nmol/L VitD+Ca-37.8 +/- 10.9 nmol/L MMN+D+Ca-36.9 +/- 12.5 nmol/L	VD (Vit D 10 µg)/day Vs. VD-Ca (Vit D 10 µg + calcium 600 mg)/day Vs. Placebo	compliance not given but 18.5% dropped out	

Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report] (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Jackson 2011 ²⁶⁸ WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Postmenopausal nd 0%	vitamin D intake: placebo- 7.54+/-6.36 ug/d, CaD- 7.42+/-5.84 ug/d calcium intake: placebo- 1049+/-625.7 mg/d, CaD- 1,039+/-635.1 mg/d	(400 IU Vit D ₃ +1000 mg elemental calcium)/day Vs. placebo	80% or greater compliance-968 women (placebo = 500, CaD= 468)
Karkkainen 2010 ²⁶⁹ OSTPRE-FPS Kuopio, Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Postmenopausal 67.4 (SD 1.9) 0%	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)	Vit D 800 IU+calcium 1,000 mg Vs. control (neither supplementation nor placebo)	79% compliance
Kukuljan 2011 ²⁷² Geelong, Australia	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 59.9 (SD 7.4) 100%	calcium intake: 911–1064 mg/d Serum vitamin D level: 86.3+/-36.0 nmol/L	fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃) vs. controls	exercise program- 63% (95% CI: 57, 69) fortified milk- 90% (95% CI, 87, 93),
Moschonis 2011 ²⁷¹ Postmenopausal Health Study Greece	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 62.4 (SD 5.3) 0%	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d	CaD (800 mg calcium+10 µg Vit D ₃)/day Vs. control	NR
Moschonis 2010 ²⁷⁰ Postmenopausal Health Study Greece	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 60.7 (SD 5) 0%	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level: 26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months Vs. control (neither counselling nor dietary products)	nd
Zhu 2008 ²⁶⁶ Beijing, China	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 10.1 (SD 0.3) 0%	Vit D intake Control group— 0.9 ± 0.6µg/d CaD milk—0.9 ± 0.6µg/d	560 mg calcium + 5- 8 µg Vit D/school day Vs. control (no supplementary milk and habitual diet)	nd

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current 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 ²⁷³ [16280447]	10–12 y girls	BMC	1°	24	Vit D 200 IU + Ca carbonate 1000 mg	46	kg	1.3	34.70%	34.3%, 35.1 %	-0.3%	-0.8, 0.2 ^A	NS	C
					Placebo	39		1.3	35.00%	34.6%, 35.4 %				
Bolton-Smith 2007 ²⁷⁴ [17243866]	Postmeno- pausal 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 _A , 15.0	NS	B
					Placebo	56		nd	0.7	-10.2, 11.6				
Zhu 2008 ²⁷⁵ Australia CIFOS [18089701]	Postmeno- pausal women	Hip BMD	1°	60	Vit D ₂ 1000 IU + Ca citrate 1200 mg	39/33 ^B	mg/cm ²	783	nd		2.20%	1.9, 2.5	0.05	B
					Placebo	41/36 ^B		828	nd					
Moschonis 2006 ²⁷⁶ [17181890]	Postmeno- pausal 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	1.50%	0.9%, 2.2%	2.20%	1.3, 3.1 ^A	<0.05	C
					Control (usual diet)	36		1.12	-0.70%	-1.4%, -0.1%				
NEW Studies														
Islam 2010 ²⁶⁷	9–18, 19–50 yrs	Femoral neck BMC	1°	1 yr	VD (Vit D 10 µg)/day	40	g	3.384	change=0.06 1	sd=0.205	+0.14	0.05, 0.22	<0.001	A
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	3.436	change=0.06 9	sd=0.174	+0.14	0.07, 0.22	<0.001	
					Placebo	35	g	3.316	change=- 0.075	sd=0.146				
		Femoral neck BMD			VD (Vit D 10 µg)/day	40	g/cm ²	0.8	change=0.01 2	sd=0.028	+0.02	0.01, 0.03	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm ²	0.799	change=0.01 3	sd=0.030	+0.02	0.01, 0.03	<0.001	
					Placebo	35	g/cm ²	0.768	change=- 0.010	sd=0.012				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

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
	Lumbar spine L2-L4 BMC	VD (Vit D 10 µg)/day			40	g	32.548	change=0.62 0	sd=2.442	+0.58	-0.84, 2.00	0.42		
		VD-Ca (Vit D 10 µg + calcium 600 mg)/day			41	g	31.782	change=0.68 7	sd=2.761	+0.65	-0.82, 2.12	0.39		
		Placebo			35	g	32.399	change=0.04 2	sd=3.673					
		VD (Vit D 10 µg)/day			40	g/cm ²	0.898	change=0.01 3	sd=0.036	+0.02	-0, 0.04	0.12		
	Lumbar spine L2-L4 BMD	VD-Ca (Vit D 10 µg + calcium 600 mg)/day			41	g/cm ²	0.895	change=0.01 0	sd=0.042	+0.01	-0.01, 0.03	0.22		
		Placebo			35	g/cm ²	0.891	change=- 0.003	sd=0.049					
		VD (Vit D 10 µg)/day			40	g	5.818	change=0.15 8	sd=0.549	+0.31	0.09, 0.53	0.01		
		VD-Ca (Vit D 10 µg + calcium 600 mg)/day			41	g	5.877	change=0.09 0	sd=0.419	+0.24	0.06, 0.43	0.01		
	Trochanter BMC	Placebo			35	g	5.885	change=- 0.151	sd=0.389					
		VD (Vit D 10 µg)/day			40	g/cm ²	0.634	change=0.00 2	sd=0.021	+0.02	0.01, 0.03	0.002		
		VD-Ca (Vit D 10 µg + calcium 600 mg)/day			41	g/cm ²	0.625	change=0.00 1	sd=0.026	+0.02	0.01, 0.03	0.01		
		Placebo			35	g/cm ²	0.619	change=- 0.017	sd=0.029					
Trochanter BMD	VD (Vit D 10 µg)/day			40	g/cm ²	0.654	change=0.01 0	sd=0.035	+0.03	0.01, 0.04	<0.001			
	VD-Ca (Vit D 10 µg + calcium 600 mg)/day			41	g/cm ²	0.654	change=0.01 5	sd=0.031	+0.03	0.02, 0.05	<0.001			
	Placebo			35	g/cm ²	0.628	change=- 0.018	sd=0.027						
	Placebo			35	g/cm ²	0.628	change=- 0.018	sd=0.027						

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

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
Jackson 2011 ²⁶⁸	Postmeno- pause	Intertrochanteri c BMD	1°	year 6	(400 IU Vit D ₃ +1000 mg elemental calcium)/day	777	g/cm ²	0.746	final=0.749	sd=0.135	+0.02	0.01, 0.04	<0.001	A
					placebo	751		0.725	final=0.725	sd=0.137				
		Narrow neck BMD			(400 IU Vit D ₃ + 1000 mg elemental calcium)/day	777		0.736	final=0.742	sd=0.133	+0.02	0.01, 0.03	0.003	
					placebo	751		0.723	final=0.722	sd=0.136				
		Shaft BMD			(400 IU Vit D ₃ + 1000 mg elemental calcium)/day	777		1.18	final=1.199	sd=0.189	+0.03	0.01, 0.05	<0.001	
					placebo	751		1.155	final=1.165	sd=0.190				
Karkkainen 2010 ²⁶⁹ OSTPRE-FPS	51–70 yrs	Femoral neck BMD	1°	3 yrs	Vit D 800 IU + calcium 1,000 mg	280	g/cm ²	0.866	final=0.848	sd=0.13	-0.002	-0.02, 0.02	0.85	C
					control (neither supplementatio n nor placebo)	311		0.865	final=0.850	sd=0.12				
		Lumbar spine BMD			Vit D 800 IU + calcium 1,000 mg	259		1.039	final=1.047	sd=0.17	0.013	-0.04, 0.02	0.37	
					control (neither supplementatio n nor placebo)	285		1.052	final=1.060	sd=0.17				
		Total body BMD			Vit D 800 IU+calcium 1,000 mg	195		1.069	final=1.078	sd=0.10	-0.003	-0.02, 0.02	0.76	
					control (neither supplementatio n nor placebo)	238		1.079	final=1.081	sd=0.10				
		Total proximal femur BMD			Vit D 800 IU+calcium 1,000 mg	280		0.948	final=0.934	sd=0.14	-0.005	-0.03, 0.02	0.65	

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

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		
Kukuljan 2011 ²⁷²	51–70, 71+ yrs	Trochanter BMD	1°	18 months	control (neither supplementatio n nor placebo)	310		0.953	final=0.939	sd=0.13						
					Vit D 800 IU+calcium 1,000 mg	280		0.783	final=0.779	sd=0.13	-0.01	-0.03, 0.01	0.31			
					control (neither supplementatio n nor placebo)	310		0.797	final=0.790	sd=0.13						
					Vit D 800 IU + calcium 1,000 mg	280		0.67	final=0.652	sd=0.14	-0.001	-0.02, 0.02	0.93			
		Ward's triangle			control (neither supplementatio n nor placebo)	310		0.672	final=0.653	sd=0.13						
		L1-L3 total volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D ₃)	45	g/cm ³	164	change=-0.6	-2.1, 0.8	-0.6	-2.7, 1.6	0.61			
					controls	44		171	change=-0.05	-1.5, 1.4				A		
					L1-L3 trabecular volumetric BMD	fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D ₃)	45		115	change=-1.5	-3.1, 0.9	-2.3	-6.4, 1.8	0.26		
						controls	44		120	change=0.8	-2.9, 1.2					
					mid-femur cortical volumetric BMD	fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D ₃)	45		1104	change=-1.0	-1.4, -0.6	-0.3	-1.0, 0.4	0.41		
						controls	44		1108	change=-0.7	-1.3, -0.2					
					mid-tibia cortical volumetric BMD	fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D ₃)	45		1105	change=-1.2	-1.7, -0.7	-0.1	-0.8, 0.6	0.78		
						controls	44		1113	change=-1.1	-1.6, -0.5					

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

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
Moschonis 2011 ²⁷¹	Postmeno- pausal Health Study	heel BMD	1°	12 months	CaD (800 mg calcium + 10 µg Vit D ₃)/day	26	g/cm ²	0.476	final=0.459	sd=0.081	-0.002	-0.04, 0.04	0.92	B
					Control	39		0.472	final=0.461	sd=0.083				
		L2-L4 BMD			CaD (800 mg calcium + 10 µg Vit D ₃)/day	26		1.121	final=1.113	sd=0.160	+0.01	-0.07, 0.10	0.77	
					control	39		1.134	final=1.101	sd=0.167				
		total body BMD			CaD (800 mg calcium+10 µg Vit D ₃)/day	26		1.112	final=1.135	sd=0.083	+0.04	0, 0.08	0.05	
					control	39		1.095	final=1.094	sd=0.079				
Moschonis 2010 ²⁷⁰	Postmeno- pausal Health Study	pelvis BMD	1°	30 months	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months	35	g/cm ²	1.096	final=1.089	sd=0.087	+0.02	-0.02, 0.06	0.30	B
					control (neither counselling nor dietary products)	31		1.067	final=1.067	sd=0.084				
		total body BMD			(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months	35		1.134	final=1.135	sd=0.067	+0.03	-0.01, 0.06	0.11	
					control (neither counselling nor dietary products)	31		1.124	final=1.106	sd=0.078				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

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
Zhu 2008 ²⁶⁶	9–18 yrs	total spine BMD	1°	2 yrs	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months	35		1.119	final=1.234	sd=0.135	+0.04	-0.03, 0.11	0.23	B
					control (neither counselling nor dietary products)	31		1.139	final=1.193	sd=0.139				
		midriff BMDsc			560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm ^{1.586}	1585	final=1803	sd=446	+43	-79, 165	0.49	
					control (no supplementary milk and habitual diet)	123	mg/cm ^{1.586}	1584	final=1760	sd=499				
		pelvis BMDsc			560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm ^{3.082}	46	final=49	sd=7	0	-1.9, 1.9	1	
					control (no supplementary milk and habitual diet)	123	mg/cm ^{3.082}	47	final=49	sd=8				
		total body BMDsc			560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm ^{2.528}	93	final=95	sd=10	+3	0.3, 5.7	0.03	
					control (no supplementary milk and habitual diet)	123	mg/cm ^{2.528}	95	final=92	sd=11				

Note: Outcomes cells are shaded for the Control rows.

^A Estimated from reported data.

^B Baseline/followup 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 **as well as a high-quality systematic review**. 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.⁸ 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

The current report identified one systematic review published since the original report that addressed the question as well as eighteen new RCTs that met the inclusion criteria (two that used fortified foods and the remainder that used supplements). The systematic review reported widely varying increases in serum concentrations of 25(OH) for similar doses of vitamin D, with a general increase in serum concentration with dietary intake.

For the original report, the updated search did not identify new RCT evaluating the effect of food fortification on serum 25(OH)D concentrations since the Ottawa EPC report.⁸ 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

The current report identified one quality systematic review that addressed the relationship between vitamin D supplementation and net change in serum 25(OH)D concentrations.²⁷⁷ This review included 76 placebo-controlled and open-label trials published from 1984 through 2011 that assessed the effects of vitamin D supplementation (most trials used oral doses, although a small number of studies administered vitamin D via injection). Doses tested ranged from 200 to 10,000IU per day. Similar doses resulted in increases in serum 25(OH)D that varied by three to

four fold. Meta-regression showed that serum concentrations increased by an average of 1.95 nmol/L for each 40IU per day supplementation; use of ergocalciferol in place of cholecalciferol resulted in smaller increases, and simultaneous supplementation with calcium resulted in non-significantly smaller increases in serum 25(OH)D concentrations. The small number of trials that used higher doses precludes assessment of whether the dose-response relationship plateaus at higher doses. Most studies did not stratify findings by sex, and the review itself did not stratify findings by assay method.

Eighteen of the RCTs that met inclusion criteria for the current report could be included in an assessment of dose response (Table 67). Two of the studies provided the Vitamin D as fortified foods;^{229,272} the remainder administered supplemental vitamin D alone or in combination with calcium.^{150,186,188,228,230,231,234-236,244,245,248,260,267,269,278} One study administered ergocalciferol.¹⁸⁸

All studies reported an increase in serum 25(OH)D with supplementation. However, the studies varied by age group and health status of participants, baseline vitamin D status, dose, duration, and assay used to assess serum 25(OH)D. Further information on assay methods and performance is provided in Appendix G.

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 are a small but representative random sample of all available data.

We plotted the net changes in serum 25(OH)D concentration against the doses of vitamin D supplementation using data from 44 RCTs with 50 comparisons in adults and children. Only RCTs of daily vitamin D₃ supplementation (doses ranged from 200 to 5000 IU/d) alone or in combination with calcium supplementation (doses ranged from 500 to 1550 mg/d) that provided sufficient data for the calculations were included 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 D₃ with increasing net change in 25(OH)D concentration was evident in both adults and children (Figure 12). It was also apparent that the dose-response relationships differ depending on study participants' serum 25(OH)D status (≤ 40 vs. >40 nmol/L) at baseline (Figure 13), and depending on duration of supplementation (≤ 3 vs. >3 months) (Figure 14). **For the current report, we also plotted the relationship between dose of vitamin D₃ and net change in 25(OH)D concentration according to the assay method reported (Figure 15).** Vitamin D₂ supplementation was more commonly used in RCTs of infants and pregnant or lactating women, than vitamin D₃ supplementation. Results showed that

supplementation of vitamin D₂ significantly increased 25(OH)D concentrations in infants, lactating mothers and in cord blood.

Detailed Presentation (Table 67; Figures 12, 13, 14, & 15)

The results from 26 RCTs with 28 comparisons in adults and two RCTs with three comparisons in children evaluating the effect of vitamin D₃ supplementation alone or in combination with calcium supplementation on serum 25(OH)D concentrations are shown in Table 67. Most of the data **included in the original report** were extracted directly from the Ottawa EPC report. In adults **included in studies from both the original and the current report**, the doses of vitamin D₃ ranged from 200 to 5000 IU/d, and the doses of calcium supplementation ranged from 500 to 1550 mg/d across the comparisons. In children, the doses of vitamin D₃ ranged from 200 to 2000 IU/d. Duration of supplementation ranged from 0.5 to 60 months. Study populations and baseline vitamin D concentrations varied across these comparisons.

Figure 15 shows the dose-response results by reported assay method. Most studies reported using a radioimmunoassay, a radioreceptor assay (a heterogeneous group, as a number of different molecules are used as receptors), or a method involving HPCL-tandem mass spectrometry; few studies reported using a chemiluminescence assay (CLIA) or enzyme linked immunoadsorption assay (ELISA). The plots show slightly different patterns for the different assays.

The remainder of this section reports the results of the dose response assessment conducted for the 2006 evidence review and described in the original report.

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% CI 11, 18) to 40 (95% 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 D₂ versus vitamin D₃. 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.

Ottawa EPC Report—Infants

Seven RCTs included infants and few trials used vitamin D₃ supplementation. One RCT concluded that 200 IU of vitamin D₂ 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 D₃/d. Three trials used 1000 IU vitamin D₂/d and one trial used 1000 IU/d of vitamin D₃. Supplementation of vitamin D₂ 1000–3600 IU/d and vitamin D₃ 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 D₂/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 D₃ per day and 400 IU of vitamin D₂. There were consistent increases in serum 25(OH)D concentrations ranging from 8 nmol/L (200 IU/d), 16.5 (with 600 IU D₃/d) to 60 nmol/L (2000 IU of vitamin D₃/d).

Ottawa EPC Report—Premenopausal Women and Younger Men

Ten small trials included premenopausal women and younger males. Three trials compared vitamin D₂ to vitamin D₃ 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 D₃ ranged from 600 to 10,000 IU/day and vitamin D₂ (4000 IU/d or 50,000 to 100,000 for single dose).

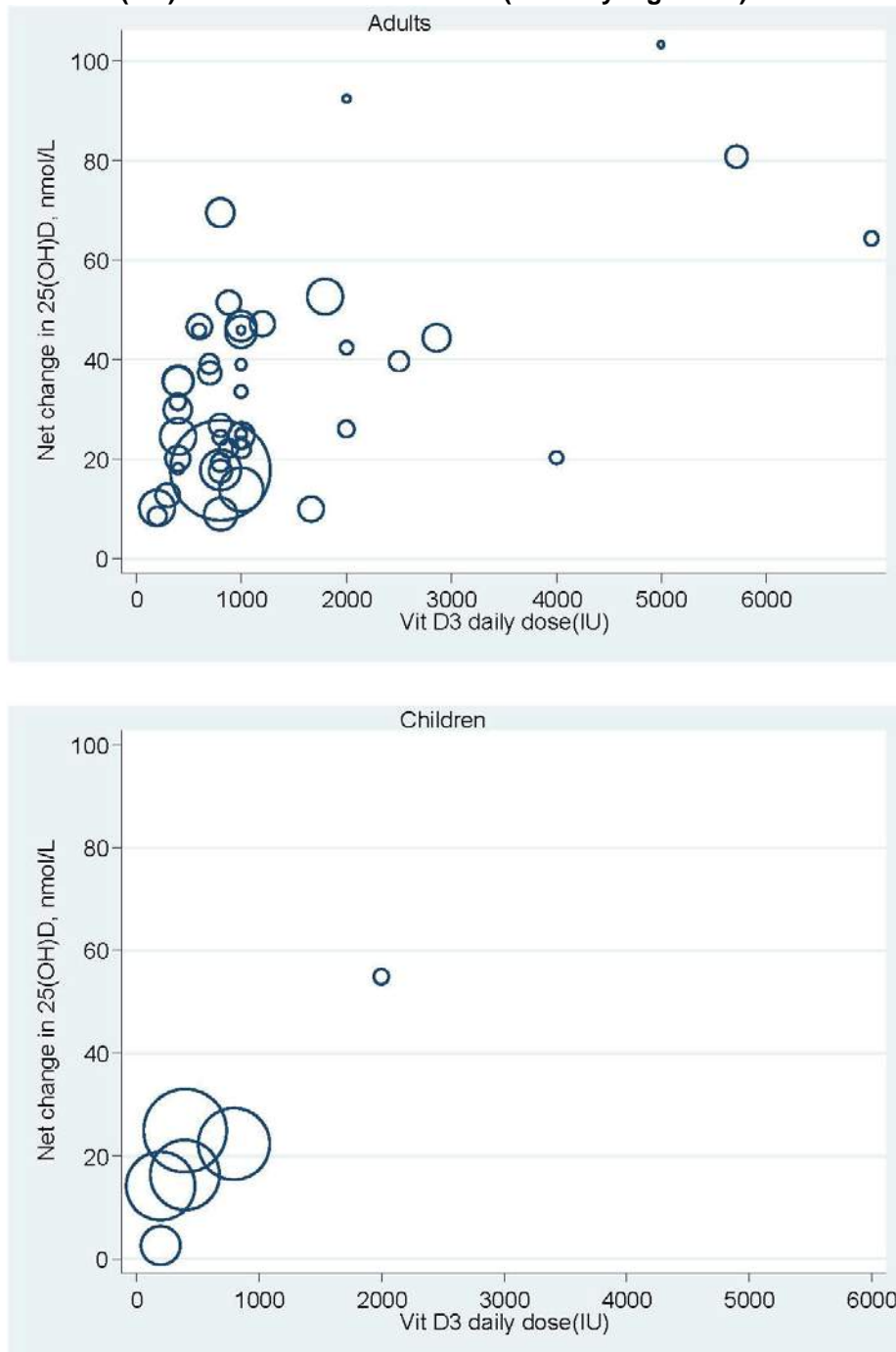
Three trials found that supplementation with vitamin D₂ and D₃ in healthy adults may have different effects on serum 25(OH)D concentrations. One trial compared 100,000 IU vitamin D₂ given orally versus injection and found a greater variability in response with the intramuscular preparation. There appeared to be dose-response effect in those trials that used multiple doses of vitamin D₃, 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 D₃ ranged from 100 to 4000 IU/day and vitamin D₂ was 9000 IU/day. One trial was conducted in African American women.

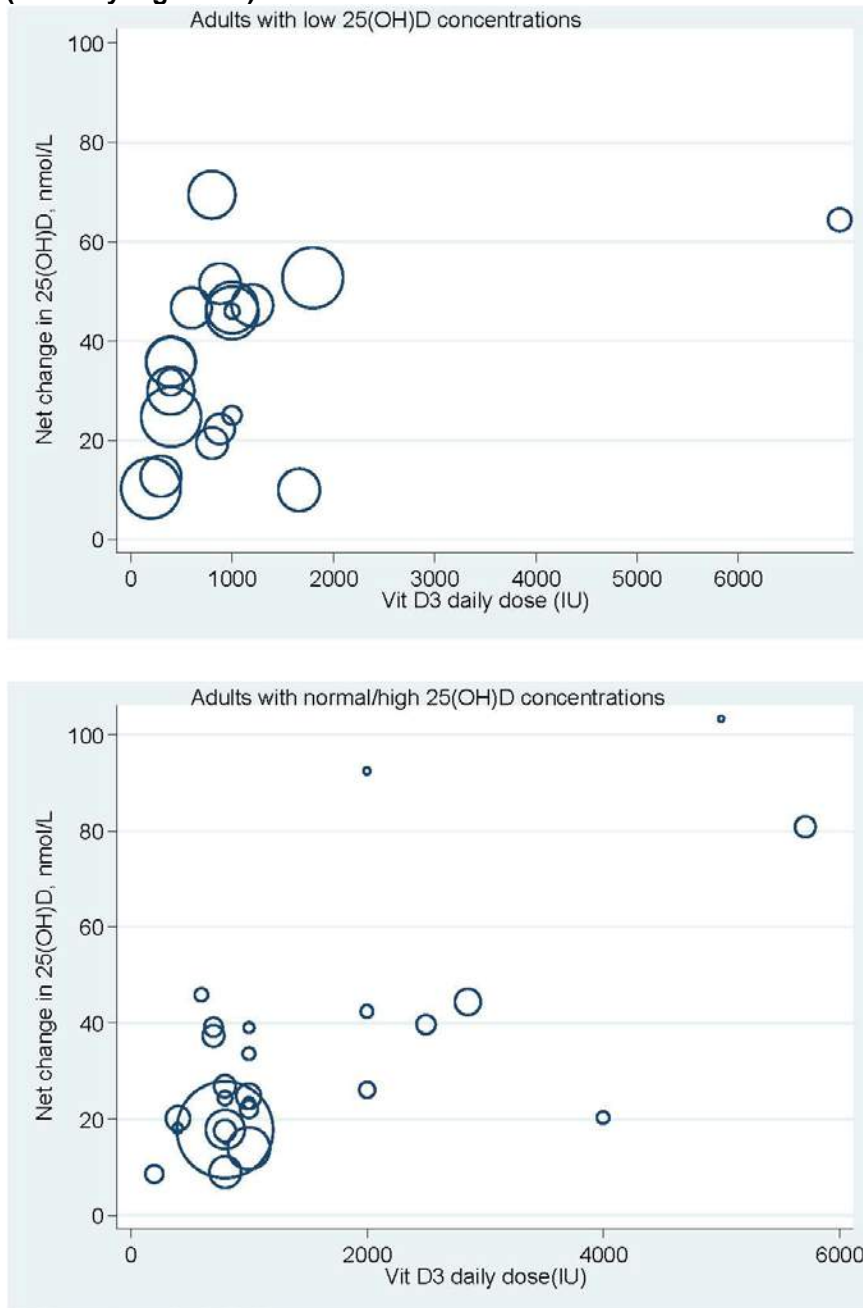
One trial found that wintertime declines in serum 25(OH)D concentrations were prevented with 500 IU vitamin D₃ per day. A dose response with increasing doses of vitamin D₃ was noted for serum 25(OH)D concentrations. There was variability in response to similar doses across trials that may have been due 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 12. Relationship between doses of vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs (formerly Figure 23)



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 13. Relationship between doses of vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults (formerly Figure 24)



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 14. Relationship between doses of vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults (formerly Figure 25)

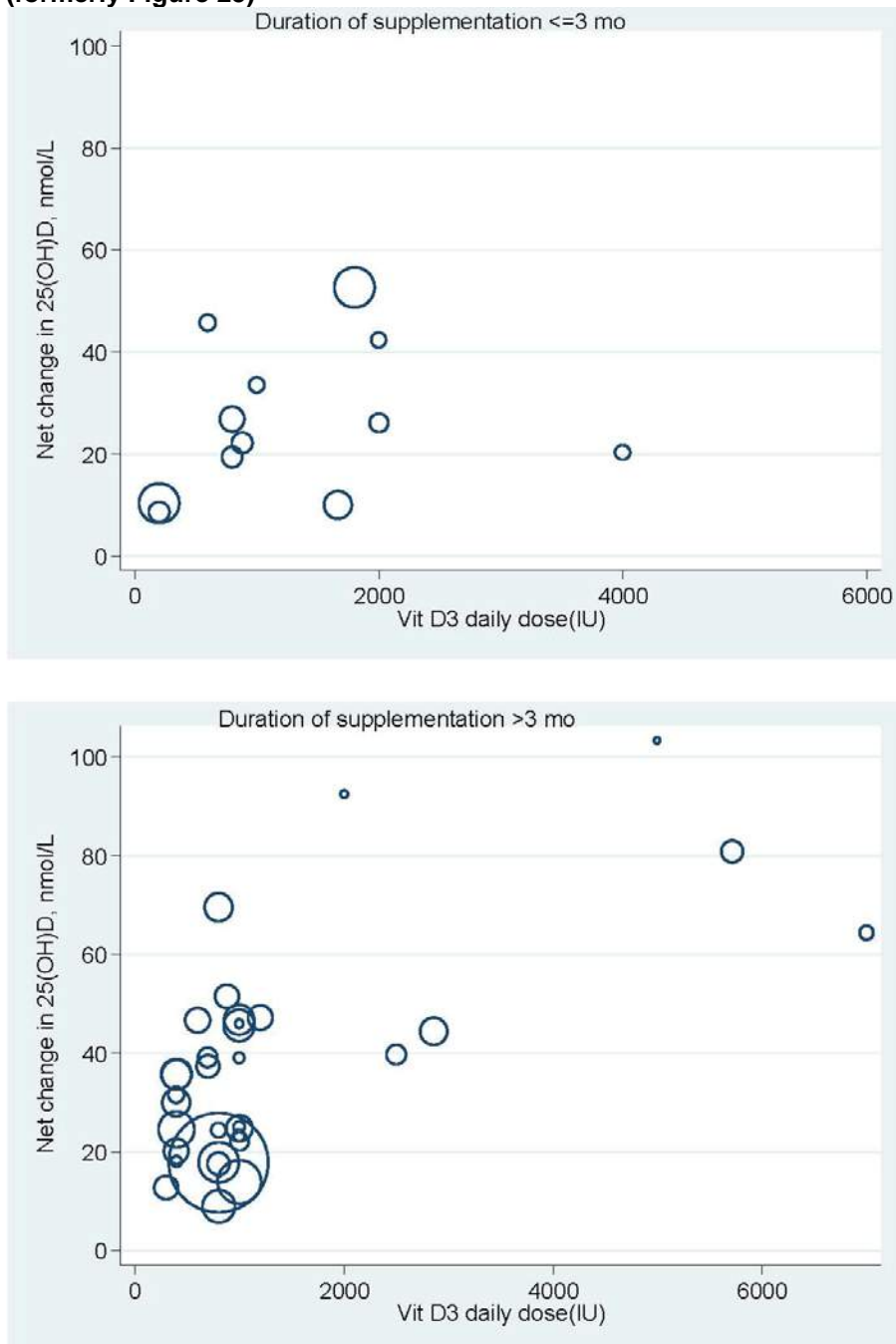
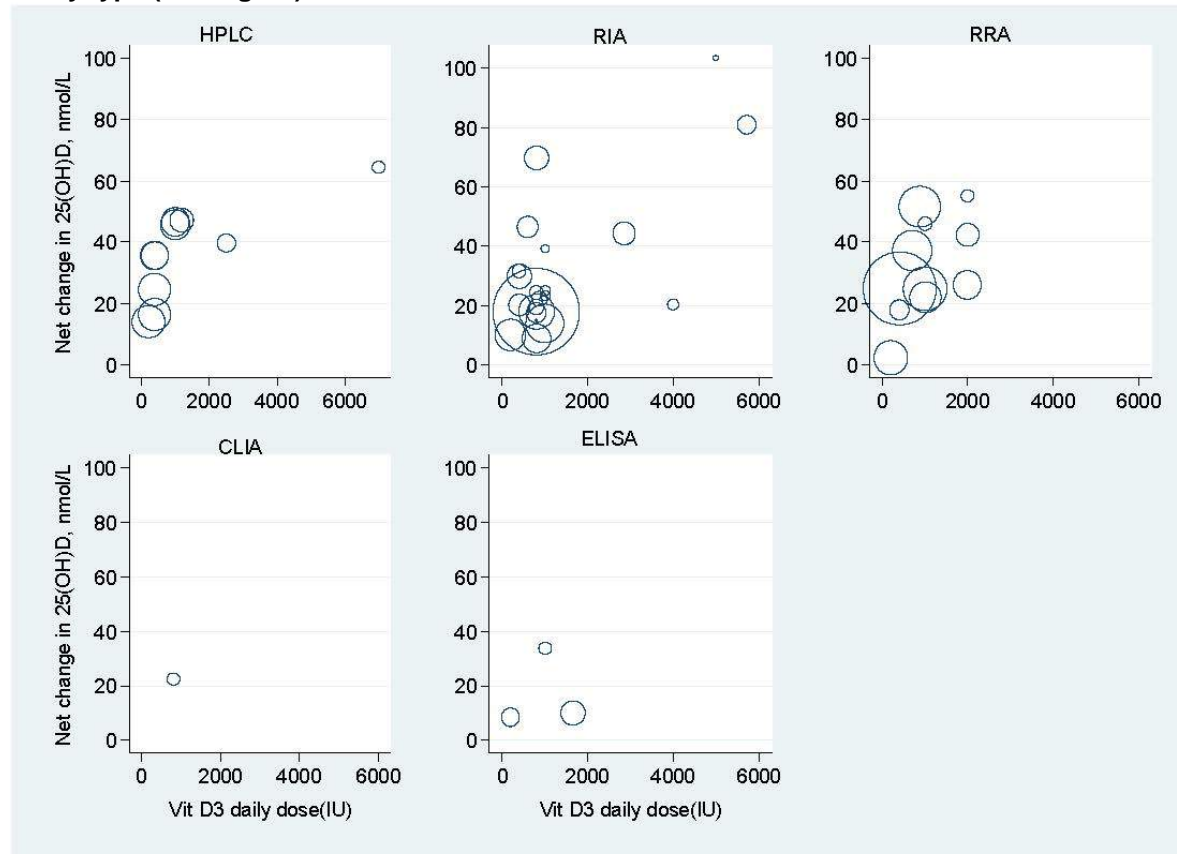


Figure 15. Relationship between doses of vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs by assay type (new figure)



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 67. The relationship between vitamin D₃ daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report)

Author/Year	Assay Method	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
New Studies												
Gaanmaa, 2012 ²⁷⁸	CLIA	9-18 yrs	17.8	800	0	6	57	31.9	11.1	55	9.6	9.7
Gepner, 2012 ²²⁹				2500 Fortified cookies								
	HPLC	Postmenopausal	78.1 (26.5)		0	4	55	39.2	23.2	55	-0.5	15.2
Islam, 2010 ²⁶⁷	RIA	19–50	36.1	400	600	12	40	32.1	23.6	35	0.5	13.8
Jorde, 2010 ²³⁰	RIA	19–50, 51–70	57.8	2857	500	12	104	42.8	22.5	112	-1.6	16.8
Jorde, 2010	RIA	19–50, 51–70	58.7	5,714	500	12	114	79.3	31.2	112	-1.6-	16.8
Karkainen, 2010 ²⁶⁹	RIA	51–70, 70+	49.6	800	1000	36	287	24.7	24.1	306	6.8	19.3
Kukuljian, 2011 ²⁷²	RIA	51–70, 71+	88.1	Fortified milk 800	500	18	45	27.5	111.1	44	12.5	109.8
Li-Ng, 2009 ¹⁵⁰	RRA	19–50, 51–70	63.7	2000	0	3	78	24.0	30.6	70	-2.1	20.9
Macdonald, 2013 ²⁴⁵				400								
	HPLC MS ²	51–70 yrs	34.6			12	84	31.6	19.8	89	-4.1	11.5
Macdonald, 2013	HPLC MS ²	51–70 yrs	34.5	1000		12	90	42.6	18.9	89	-4.1	11.5
Molgaard, 2010 ²⁴⁸	HPLC MS ²	9–11 yrs	42.6	200	0	12	73	11.0	10.3	74	-3.1	9.8
Molgaard, 2010	HPLC MS ²	9–11 yrs	40.0	400	0	12	74	13.3	10.8	74	-3.1	9.8
Nieves, 2012 ²⁴⁴	RIA	Postmenopause	29.0	1000	≤1000	24	55	26.0	41.4	48	1.0	12.5
Pfeiffer, 2009 ¹⁸⁶	RIA	71+ yrs	54.5	800	1000	20	121	-7	17.1	121	-16	16.8
Salehpour, 2012 ²³⁴				1000								
	ELISA	19–50 yrs	41.9 ()		0	3	39	38.2	32	38	4.6	14
Salovaara, 2010 ²⁶⁰				800								
	RIA	51–70, 71+ yrs	49.5		1000	36	1586	24.6	20.5	1609	6.8	20.1
Toxqui, 2013 ²²⁸	ELISA	9–50 yrs	62.6	200		2	55	8.9	21.0	54	0.3	19.7
Wamberg, 2013 ²³⁶				7000								
	HPLC MS ²	9–50 yrs	33.5			6.5	22	77.2	18.4	21	12.8	15.0
Witham, 2013 ²³⁵	ELISA	9–71+ yrs	27	1667		2	25	10	10.2	25	0	10.2
Wood, 2012 ²³¹	HPLC MS ²	Postmenopause	34.5	400	0	12	84	33.0	20.2	91	-2.7	12.4
Wood, 2012	HPLC MS ²	Postmenopause	30.3	1000	0	12	90	42.9	19.0	91	2.7	12.4
Zhu, 2010 ¹⁸⁸				D2:								
	RIA	71+ yrs	44.7	1000	1000	12	129	14.7	13.3	132	0.8	13.2

Table 67. The relationship between vitamin D₃ daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report) (continued)

Author/Year	Assay Method	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
Old Studies												
Bjorkman 2008 ²⁶³	HPLC	71+	23	400	0	6	60	26.5	11.8	59	1.9	10.2
Bjorkman 2008 ²⁶³	HPLC	71+	23	1200	0	6	63	49.1	19.5	59	1.9	10.2
Blum 2008 ²⁷⁹	ND	71+	73	700	500 ^A	12	132	48.5	35.3	125	9.3	21.5
Bunout 2006 ¹⁸³	RIA	71+	40	400	800 ^A	9	46	33.4	14.3	46	3.5	10.0
Chapuy 1992 ²⁸⁰	RIA	71+	36	800	1200	18	73	65.0	16.5	69	-4.5	13.5
Chel 2008 ²⁸¹	RIA	71+	23	600	0	4	46	46.9	15.4	45	0.3	12.2
Deroisy 2002 ²⁸²	RIA	71+	28	200	500 ^A	3	50	14.7	10.0	50	4.5	10.0
Himmelstein 1990 ²⁸³	RRA	71+	45	2000	0	1.5	15	39.7	15.7	15	-2.7	13.4
Kenny 2003 ²⁸⁴	RRA	71+	62	1000	500 ^A	6	29	22.3	10.1	31	-2.5	11.4
Krieg 1999 ²⁸⁵	RRA	71+	29	880	500	24	34	36.5	14.0	38	-15.0	11.1
Pfeifer 2000 ²⁸⁶	RIA	71+	25	880	1200 ^A	2	74	40.5	27.0	74	18.3	20.9
Pfeifer 2001 ²³⁸	RIA	71+	25	800	1200	2	73	39.2	22.4	72	19.7	23.8
Sorva 1991 ²⁸⁷	RRA	71+	11	1000	1000	10	5	44.6	28.9	10	-1.4	2.3
Zhu 2008 ²⁷⁵	RIA	71+	68	1000	1200 ^A	60	29	36.2	27.5	34	-2.9	27.4
Barnes 2006 ²⁸⁸	Not available	adults	52	600	1500 ^A	2	12	38.6	15.1	15	-7.2	11.3
Bolton-Smith 2007 ²⁷⁴	RIA	adults	60	400	100	24	50	12.0	15.1	56	-8.2	14.3
Dawson-Hughes 1997 ²⁸⁹	RRA	adults	74	700	500	36	145	35.2	32.6	167	-2.1	22.7

Table 67. The relationship between vitamin D₃ daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report) (continued)

Author/Year	Assay Method	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
Harris 2002 ²⁹⁰	HPLC/RRA	adults	55	800	0	2	27	22.3	14.0	23	-4.6	6.3
Heaney 2003 ²⁹¹	RIA	adults	71	1000	0	5	16	12.0	16.0	16	-11.4	17.6
Heaney 2003 ²⁹¹	RIA	adults	71	5000	0	5	17	91.9	37.6	16	-11.4	17.6
Heikkinen 1998 ²⁹²	HPLC/RRA	adults	26	300	500 ^A	12	18	9.4	10.9	18	-3.3	6.4
Honkanen 1990 ²⁹³	Not available	adults	31	1800	1550	2.75	55	39.5	12.1	60	-13.1	9.2
Jensen 2002 ²⁹⁴	RRA	adults	41	400	1450	36	33	34.6	23.2	33	16.5	28.2
Nelson 2009 ²⁹⁵	RIA	adults	62	800	0	12	55	35.3	23.2	31	10.9	16.9
Orwoll 1988 ²⁹⁶	RRA	adults	58	1000	1000	12	46	25.0	19.1	46	3.0	19.1
Patel 2001 ²⁹⁷	RIA	adults	72	800	0	12	35	8.4	13.1	35	-9.2	12.8
Riis 1984 ²⁹⁸	Not available	adults	41	2000	500	12	8	87.5	14.1	7	-5.0	23.8
Trang 1998 ²⁹⁹	RIA	adults	42	4000	0	0.5	24	23.3	17.5	24	3.0	19.8
Chan 1982 ³⁰⁰	RRA	children	43	400	0	6	30	22.5	6.6	30	-2.5	6.6
El-Hajj (Fuleihan) 2006 ⁴⁸	RRA	children	35	200	0	12	58	7.5	19.8	55	5.0	18.8
El-Hajj (Fuleihan) 2006 ⁴⁸	RRA	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 modified to fit each RCT in one line. RRAs and RIAs represent multiple procedures or commercial assay kits.

Stratification of Key Outcomes by Vitamin D Assay Method

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

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

As described in the original report, the WHI trial on women aged 50 to 79 years examined the effect of vitamin D₃ 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% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.¹³¹ 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% consumed less than 800 mg/d, 26% consumed 800 to 1200 mg/d, and 40% 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 for the original report that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

For the current report, two studies assessed the occurrence of nephrolithiasis among participants in RCTs that administered approximately 1100²⁰¹ and 2000IU¹⁵⁰ per day supplemental vitamin D without calcium. No incidents of nephrolithiasis were reported in either study.

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 the original report, 47 did not report information on adverse events. **Among 47 RCTs included in the current study, most did not include any information on adverse events.**

For the current report, one study, which administered 2000 or 4000IU per day to 504 pregnant women, reported no adverse events during the interventions.⁴² Three studies reported on only one specific outcome, hypercalcemia/serum calcium, or reported on this outcome and stated no other AEs were reported.^{1,187,239} Supplementation ranged from 400 to 5000IU per day in these studies; only 1 case of hypercalcemia was reported across all 4 of the studies, in a trial that administered 1000IU per day plus 1000mg calcium.¹⁸⁷ Seven other studies that assessed hypercalcemia also reported no cases.

Five studies reported on gastrointestinal symptoms,^{150,151,235,236,269} of which only one included supplemental calcium. Two studies reported on serious adverse events, including one death, cancer diagnoses, and acute surgeries, which were more prevalent in the placebo group and thus could not have been related to the use of vitamin D.^{152,201}

For the original report, five RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods.^{48,96,290,301,302} Of these, one RCT administered combination of vitamin D₂ (1600 or 3600 IU/d) and vitamin D₃ (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 D₃ supplement (120,000 IU sachets given 3 times, every 2 weeks, for 6 weeks), and one RCT administered 1200 IU/d vitamin D₂ supplement for 5 years.

Eleven RCTs reported at least one adverse event (Table 68). 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 D₃ or ranged from 5000 to 10,000 vitamin D₂) and/or calcium supplementations (doses ranged from 200 to 1500 mg/d) reported few cases of gastrointestinal disruption (such as constipation, diarrhea, or upset stomach), musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi. 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).¹⁸³ 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.²⁴⁷ 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 D₃ 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% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.¹³¹

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 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
New Studies					
Wamberg ²³⁶	52	7000IU/d	0	26 wks	Intervention group: 13 reports of side effects Control group: 17 reports of side effects Side effects included constipation, nausea, tiredness, and headache No participants developed symptomatic hypercalcemia
Witham ²³⁵	50	100,000IU single dose	0	8 wks	Intervention group: 3 headaches, 1 complaint of diarrhea, 1 constipation, 1 urinary tract infection, 1 complaint of joint pains, 1 subconjunctival hemorrhage Control group: 2 headaches, 2 complaints of constipation, 1 vomiting, 1 diarrhea, 1 skin rash, 1 corneal ulcer, 1 menorrhagia, 1 chest wall pain, 1 insomnia No deaths, hospitalizations, or cases of hypercalcemia or renal calculi
Wagner ⁴²	504	2000, 4000IU/d	0	Throughout pregnancy	None found
Laaksi ¹⁵¹	164	400IU/d	0	5 mos	Intervention group: 2 withdrawals because of stomach ache, nausea, diarrhea Control: 1 case facial rash
Karkainen ²⁶⁹	593	800IU/d	1000mg	3 yrs	17/290 withdrawals due to AEs: GI symptoms(9), exacerbation of diseases(2), mouth irritation, skin symptoms, nausea, cough, backache, weight increase (one each)
Prince ¹⁸⁷	302	1000IU/d	1000mg	1 yr	1 case mild hypercalcemia in intervention group
Holmund, 2012 ²³⁹	113	400, 1200, 1600IU/d	0	2.5 mos	No hypercalcemia in any arm; AEs assessed with pre-specified survey but none reported
Iuliano-Burns ²⁴²	110	50,000IU/mo (~1600IU/d) vs. 50,000IU alternate months vs. single 50,000IU dose	0	1 yr	No cases of vitamin D toxicity or hypercalcemia

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)		
Li-Ng ¹⁵⁰	162	2000IU/d	0	3 mos	AE	Vitamin D	Placebo
					GI	7	6
					Musculoskeletal	5	5
					Chest pain	1	2
					Palpitations	1	0
					Infection	8	8
					Headache	2	0
					Dizziness	1	0
					Allergic rhinitis	10	6
					Falls	0	2
					Fatigue	2	1
					Skin changes	1	4
					Nephrolithiasis	0	0
					hypercalcemia	0	0
Lips ²⁰¹	226	8,000IU/week	0	4 mos	Clinical AEs	Vitamin D	Placebo
					One or more	24	26
					Serious	3	3
					Drug related	1	4
					Deaths	1	0
					Renal stones	0	0
Hollis 2011 ¹	494	400, 2000, 4000IU/d	0	Up to 8 mos	No differences in serum calcium, no specific AEs reported		
Roth ⁴⁴	160	5000IU/d	0	3 mos	Neonatal clinical AEs: Serious nonfatal AEs: Vitamin D: 6 Placebo:7 Neonatal deaths: Vitamin D:1 Placebo: 3 Hypercalcemia: Vitamin D: 0 Placebo: 0		
Grimnis 2012 ²⁴¹	297	800 IU/d vs. 20,000 IU 2x per week (average daily dose of 6,500	1000	1 yr	No difference in total AEs reported between groups or in organ-specific AEs, no significant difference in rate of hypercalcemia or hyperphosphatemia		
Murdoch ¹⁵²	322	200,000IU1st and 2 nd month, 100,000IU monthly	0	18 mos	SAEs	Vitamin D	Placebo
					Cancer diagnosis/tx	4	1
					Surgical procedure	3	5
					Acute		
					Elective	8	5
					Trauma	3	6
					Treatment for medical condition	3	2
					Hypercalcemia	0	0

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
Original Studies					
Yamamoto 1995 ³⁰³	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 ²⁷⁶	112	300 D ₃	600 or 1200	12 mo	Bloating, constipation and intestinal discomfort apparently related to the calcium supplement
Bunout 2006 ¹⁸³	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 ¹³¹	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 ¹⁸⁴	205	800 D ₃	1200	Median 1 mo	Hypercalcemia (n=2)
Lappe 2008 ²⁵⁹	5201	800	200	8 wks	GI disruption such as constipation, diarrhea, upset stomach (4%), and musculoskeletal soreness (0.9%)
Brooke 1980 ⁴⁷	126	1000	0	3rd trimester only	Vit D group (hypocalcemia, n=0), placebo group (hypocalcemia, n=5)
Lappe 2007 ¹⁰²	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 ³⁰⁴	65	5000 or 10,000 D ₂	500	3 mo	Hypercalciuria (n=1) in control group
Zhu 2008 ²⁴⁷	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.

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
Sneve 2008 ⁹⁵	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.

Discussion

This evidence report on vitamin D and calcium in relation to health outcomes was prepared—and subsequently updated—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.

The following statements in plain type derive from the original report. Statements pertaining to the current report follow those conclusions and are in boldface type. The original report identified 165 (**126 in the current report**) primary articles that met the eligibility criteria established by the TEP. In addition, **the original report** included 11 (**3 in the current report**) 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. **The studies identified for the current report also were characterized by the same challenges.**

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). **Calcium supplementation alone was not considered for the current report.**

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. **Body weight was not considered for the current report, with the exception of birth weight. The number of studies that reported birth weight was too small (both in size and volume) to make any statement regarding the effect of interventions of vitamin D with or without calcium on this outcome.**

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. **Childhood growth was not considered as an outcome for the current report. The number of studies that reported prenatal growth as an outcome was too small to make any statements regarding the effect of interventions of vitamin D with or without calcium.**

For bone health, one well-conducted systematic review of RCTs found that vitamin D₃ (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. **Of the studies identified for the current report, one of seven RCTs of vitamin D supplementation alone and six of seven RCTs of vitamin D plus calcium found**

increases in BMC/BMD: The study of vitamin D alone that reported a positive effect enrolled infants, whereas the studies of vitamin D and calcium primarily enrolled postmenopausal women; the study that reported no effect of administering both vitamin D and calcium enrolled only men.

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. **Studies of calcium alone were not included in the update report.**

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). **Studies of calcium alone were not included in the update report.** 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. **Studies identified for the current report that assessed associations between cardiovascular events and serum 25(OH)D concentrations reported inconsistent results.**

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 United States, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1000 mg. **Again, studies of calcium only were not included in the current report.**

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectal, pancreatic, 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. **One high-quality systematic review that included some of the studies reviewed in the original report and some in the current report found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.**

Strengths of This Report

The strengths of this report—the **original and the update**—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 the Methods chapter 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, **both the RAND and the Tufts EPC** have conducted a number of nutrition-related evidence reports,^{23-26,305} **and Tufts** has conducted the mock exercise on vitamin A panel.⁵ 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://ndb.nal.usda.gov>) and notably missing are foods recently fortified with vitamin D.³³ 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, and 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. **The original report** 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.

For the current study, we abstracted the methods used to assay serum 25(OH)D for all RCTs included in the assessment of dose-response, as well as the RCTs included in the original report. To track the assay methods more completely, we also noted the country and the year in which the assay was performed, when reported; however, very few studies reported the year assays were conducted. Combined with the evidence regarding the significant effect of season of blood draw on serum 25(OH)D concentrations, this lack of information on year of assay renders comparing or combining outcomes challenging, even when the same type of assay was used.

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). **The searches conducted for the current report identified over 5,000 potentially relevant studies released since the completion of the original report in 2009.** Without unlimited time and resources, the systematic review conducted in this **report and the original** 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 errors³⁰⁶ 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 the AMSTAR³⁴ 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 outcomes 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 studies⁴⁰ and nutrition reporting items that we believe should be considered in quality assessment. This checklist, however, has not been calibrated and the intra- and inter-rater variability have not been assessed. We should also remind readers that impeccable study reporting does not equate to 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 DRIs. We, therefore, were unable to structure our report strictly according to pre-specified life stages. When a study enrolled populations that spanned 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 has 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 form of immunoassay to measure the serum 25(OH)D concentration, a minority used competitive protein-binding assay, **and at least for the current report, some identified studies used HPLC/tandem mass spectrometry.** Some studies reported a substantial proportion of the frozen sera were accidentally thawed and limited the analyses that could be performed, **most studies omitted reporting the length of time between sample collection and assay, and studies differed regarding whether case (or intervention) samples and control samples were assayed simultaneously.** It is unclear how this heterogeneity of sample handling 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 also 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.

The issue of compliance with supplement use is a major concern in interpreting the results of RCTs. This issue is exemplified by the results of two RCTs (reported in one article) on the effects of vitamin D supplementation during pregnancy on pregnancy complications, in which vitamin D supplementation itself was not associated with a lower risk for preeclampsia, but risk for preeclampsia was significantly associated with maternal serum 25(OH)D concentrations.⁴² Similarly, accounting for adherence had a significant impact on the effect size for fracture risk reduction in the WHI.²

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 were derived from RCTs reviewed in a systematic review of bone health in postmenopausal women **and RCTs identified for (and included in) the current report that assessed outcomes of interest, most of which pertained to older populations.** 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. **Furthermore, the current report identified a recent, quality systematic review/meta-analysis that examined this question in 75 RCTs and obtained similar results.**

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 factors like population attributable risk, morbidity, and others) for possible inclusion would be valuable.

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Abbreviations

1,25(OH) ₂ D	Calcitriol
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
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
Dx	Diagnosis
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 Followup Study
HPLC	High pressure liquid chromatography
HR	Hazard ratio
ht	Height
HT	Hormone (replacement) therapy
HTN	Hypertension
IA	Islet Autoimmune

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)
MS	Multiple sclerosis
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 Followup 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
OS	Observational Study
PAHSG	Princess Anne Hospital Study Group, U.K.
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
RA	Rheumatoid arthritis
RCT	Randomized-controlled trial
RDA	Recommended dietary allowance
RIA	Radioimmunoassay
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGA	Small-for-gestational-age
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Subgp	Subgroup

Suppl	Supplement(s)
TEP	Technical Expert Panel
TIA	Transient ischemic attack
TOHP	Trials of Hypertension Prevention
TOO	Task order officer
UK	United Kingdom
UL	Tolerable upper intake levels
U.S.	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	Madrid, Spain Beijing, China
39° N	Washington, DC St Louis, Missouri Sacramento, California	
38° N	Louisville, Kentucky 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. Efficacy Search in Medline®

Database: Ovid MEDLINE®, 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[®], 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

2013 UPDATE SEARCH METHODOLOGIES

EFFICACY SEARCH IN MEDLINE®

DATABASE SEARCHED & TIME PERIOD COVERED:

Medline® on OVID – 1/1/2013-12/30/2013

LANGUAGE:

English

SEARCH STRATEGY:

exp Vitamin D/ or (25-hydroxy vit\$ D or plasma vit\$ D or 25OHD or 25-OHD).mp. or (25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3”).tw. or (“25(OH)D” or “25-(OH)D” or “25-OH-D”).tw. or 25-hydroxycholecalciferol.tw. or 25-hydroxyergocalciferol.tw. or calcidiol.tw. or Calcifediol/ or (vit\$ adj (d or d2 or d3)).mp. or Ergocalciferols/ or Ergocalciferol\$.tw. or Cholecalciferol/ or Cholecalciferol\$.tw. or calciferol.tw.

AND

(randomized controlled trial or controlled clinical trial).pt. or randomized controlled trials/ or Random Allocation/ or Double-blind Method/ or Single-Blind Method/ or clinical trial.pt. or Clinical Trials.mp. or exp Clinical Trials/ or (clinic\$ adj25 trial\$).tw. or ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw. or Placebos/ or placebo\$.tw. or random\$.tw. or trial\$.tw. or (latin adj square).tw. or Comparative Study.tw. or exp Evaluation studies/ or Follow-Up Studies/ or Prospective Studies/ or (control\$ or prospectiv\$ or volunteer\$).tw. or Cross-Over Studies/

NOT

addresses or autobiography 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

NOT

(animals not human).sh.

SEARCH #2 - UPPER LIMIT:

DATABASE SEARCHED & TIME PERIOD COVERED:

Medline® on OVID – 1/1/2013-12/30/2013

LANGUAGE:

English

SEARCH STRATEGY:

exp Vitamin D/ or (25-hydroxy vit\$ D or plasma vit\$ D or 25OHD or 25-OHD).mp. or (25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3”).tw. or (“25(OH)D” or “25-(OH)D” or “25-OH-D”).tw. or 25-hydroxycholecalciferol.tw. or 25-hydroxyergocalciferol.tw. or calcidiol.tw. or Calcifediol/ or (vit\$ adj (d or d2 or d3)).mp. or Ergocalciferols/ or Ergocalciferol\$.tw. or Cholecalciferol/ or Cholecalciferol\$.tw. or calciferol.tw.

AND

supplement\$.tw. or exp Dietary Supplements/to, ae, po, ut or No-Observed-Adverse-Effect Level/ or upper limit\$.tw. or UL.tw. or (excess\$ or toxic\$).tw. or vit\$ d intoxic\$.tw. or (noel or noel).tw. or (no observed adj2 effect\$).tw.

AND

heterotopic ossification.mp. or exp Ossification, Heterotopic/ or myositis ossificans.mp. or exp Myositis Ossificans/ or calcinosis.mp. or exp Calcinosis/ or extraosseous calcification.mp. or metaplastic calcification.mp. or myo-osteosis.mp. or neurogenic osteoma.mp. or osseous heteroplasia.mp. or ossifying fibromyopathy.mp. or para-articular calcification.mp. or heterotopic calcification.mp. or synostosis.mp. or ectopic bone.mp. or heterotopic bone.mp. or dystrophic ossification.mp. or ectopic ossification.mp. or metaplastic ossification.mp. or para-articular ossification.mp. or soft tissue calcification.mp. or (vascular adj3 calcification).mp. or (aort\$ adj3 calcification).mp. or (valv\$ adj3 calcification).mp. or (pathological bone or pathological calcification or periarticular calcification).mp. or (periarticular ossification or pathological ossification or ectopic calcification).mp. or Calcification, Physiologic/de or Hypercalcemia/ or Kidney Calculi/ or Nephrocalcinosis/ or Urinary Calculi/ or Bladder Calculi/ or Ureteral Calculi/ or Calcinosis/ or Hypercalcemi\$.tw. or (Burnett\$ adj2 syndrome\$).tw. or Hypercalciuri\$.tw. or psoriasis.mp. or exp Psoriasis/

NOT

*Dialysis/ or *hemodialysis/ or *peritoneal dialysis/

NOT

addresses or bibliography or biography or case reports or comment or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news

SEARCH #3:

**DATABASE SEARCHED & TIME PERIOD COVERED:
COCHRANE TRIALS, SYSTEMATIC REVIEWS, AND OTHER REVIEWS
DATABASES 1/1/2013-12/31/2013**

LANGUAGE:

English

SEARCH STRATEGY:

“Vitamin D” or 25-hydroxy vit* D or “25-hydroxyvitamin d” OR plasma vit* D or 25OHD or 25-OHD or 25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3” or “25(OH)D” or “25-(OH)D” or “25-OH-D” OR 25-hydroxycholecalciferol or 25-hydroxyergocalciferol or calcidiol or (vit* adj (d or d2 or d3)) or Ergocalciferol* or Cholecalciferol* or calciferol* in Title, Abstract, Keywords

Appendix B. Search Strategy for Systematic Reviews

Databases: MEDLINE[®], 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 C. Evidence Tables for the Current Report

List of Abbreviations and Acronyms Included in Evidence Tables

Abbreviation	Term
ACS	Aortic calcification score
ADL	Activities of Daily Living
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
CHS	Cardiovascular Health Study
CKD	Chronic kidney disease
CRC	Colorectal cancer
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTHER	EStrogen and THromboEmbolism Risk Study
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HPFS	Health Professionals Follow-Up Study
HR	Hazard ratio
InChianti	Invecchiare nel Chianti
INTAPP	International Trial of Antioxidants in the Prevention of Pre-eclampsia
InChianti	Invecchiare nel Chianti
KORA	Cooperative Health Research in the Region Augsburg
InChianti	Invecchiare nel Chianti

Abbreviation	Term
LDL	Low-density lipoprotein
MEC	Mobile Examination Center
MESA	Multi-ethnic Study of Atherosclerosis
MI	Myocardial infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease Study
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease Study
NSAIDS	Non-steroidal anti-inflammatories
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PASE	Physical Activity Score For The Elderly
PTH	Parathyroid hormone
Q	Quartile
RR	Relative risk
SC	Size-corrected
SD	Standard deviation
SBP	Systolic blood pressure
SES	Socioeconomic status
SPPB	Secondary-Short Physical Performance Battery
TUAG	Timed Up and Go
VTE	Venous thromboembolism
YRS	Years

Vitamin D Update Evidence Table

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Afzal et al., 2013	Prospective Cohort	19–50 years; 51–70 years; free of cancer; 20–100 years of age	Not specified		hospital	Denmark	9791/9791/55	58/47–65		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Afzal et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Tobacco Consumption In Pack-Years, Alcohol Consumption In Grams Per Week, Level Of Leisure Time, Work-Related Physical Activity; Other - Competing Risk Of Death	Primary-All Cancer	25(OH)D	50% reduction in plasma levels	28 yrs	2488/9791	adjusted/HR	1.06	1.02, 1.11	
				Primary-Pancreatic Cancer	25(OH)D	50% reduction in plasma levels	28 yrs	109/9791	adjusted/HR	1.05	0.84, 1.30	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Afzal et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Almquist et al., 2010	Nested Case Control	19–50 years; 51–70 years; women	Not specified	Malmo Diet and Cancer Study	Private Foundation	Malmo, Sweden	1528/745/100	57 (7.2)/NR		Post menopausal; Other; pre- and peri-menopausal	quartile of mean 25OHD2: 16.2, 20.0, 22.7, 26.2 quartile of mean 25OHD3: 45.2, 62.0, 73.7, 93.4 quartile of total 25OHD: 57.5, 80.3, 96.3, 126.1

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Almquist et al., 2010	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, SES; Anthropometrics- BMI; Medical Conditions- Menopausal Status; Sun Exposure- Screening Season; Smoking, Other Lifestyle Factors- Smoking Status, Alcohol Consumption	Primary- Breast Cancer	25(OH)D3	Quartile 1(<=70nmol/l)	7.0 years	NR/213	adjusted/OR	1	reference	0.710
					25(OH)D3	Quartile 2 (71–86nmol/L)	7.0 years	NR/164	adjusted/OR	0.84	0.60, 1.15	
					25(OH)D3	Quartile 3(87–105nmol/L)	7.0 years	NR/176	adjusted/OR	0.84	0.60, 1.17	
					25(OH)D3	Quartile 4(>=106nmol/L)	7.0 years	NR/192	adjusted/OR	0.93	0.66, 1.33	
					25(OH)D2 +D3	Quartile 1(<=71nmol/l)	7.0 years	NR/191	adjusted/OR	1	reference	0.780
					25(OH)D2 +D3	Quartile 2 (72–87nmol/L)	7.0 years	NR/170	adjusted/OR	0.95	0.68, 1.31	
					25(OH)D2 +D3	Quartile 3(88–106nmol/L)	7.0 years	NR/183	adjusted/OR	0.94	0.68, 1.32	
					25(OH)D2 +D3	Quartile 4(>=107nmol/L)	7.0 years	NR/191	adjusted/OR	0.96	0.68, 1.37	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Almquist et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Anderson et al., 2010	Prospective Cohort	The presence of at least one Vit D measurement from 2000 to 2009 in the electronic medical record	Not specified		Private Foundation	USA; Murray UT	41,504/ 41504/ 74.8	55 (21)/NR		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR, RR, HR, %)	Result	95% CI	P-val
Anderson et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)—Age, Gender; Medical Conditions—Type 2 Diabetes, Hyperlipidemia, Hypertension, Peripheral Vascular Disease	Secondary-Hypertension	serum 25(OH)D	very low (Vit D level \leq 15 ng/ml)	1.3 yrs on average	7848/ 15121	adjusted/HR	1.62	1.38, 1.89	P < 0.0001
					serum 25(OH)D	low (Vit D level 16–30 ng/ml)	1.3 yrs on average	8530/ 19474	adjusted/HR	1.18	1.05, 1.33	P = 0.005
					serum 25(OH)D	normal (Vit D level > 30 ng/ml)	1.3 yrs on average	2750/ 6909	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Anderson et al., 2010	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Aregbesola et al., 2013	Prospective Cohort	51–70 years; age 53–73 years	Current cancer; pneumonia, lung tuberculosis, bronchial asthma, chronic bronchitis	Kuopio Ischemic Heart Disease Risk Factor (KIHD) study	Government	Finland; Kuopio	1421/ 1421/ 49.1	62.5 (6.5)/ NR		Not Reported	mean serum 25(OH)D3: 43.5 nmol/l (SD: 17.8)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Aregbesola et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- Body Mass Index; Sun Exposure- High Sun Exposure At Baseline Sampling; Smoking, Other Lifestyle Factors- Smoking, Leisure Time Physical Activity; Other - Year Of Education And Income, Occupation	Primary- Pneumonia	25(OH)D3	Tertile 1: 8.9–33.8	9.8 yrs	38/925	adjusted/HR	2.4	1.2, 4.9	0.021
					25(OH)D3	Tertile 2: 33.9–50.7	9.8 yrs	22/426	adjusted/HR	1.4	0.7, 2.8	
					25(OH)D3	Tertile 3: 50.8–112.8	9.8 yrs	13/70	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Aregbesola et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	reference 9: http://rd.springer.com/article/10.1007/s00394-010-0138-3 #page-1

Eligibility Criteria and Baseline Characteristics											
Author ,Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Baker et al., 2010	Nested Case Control	Pregnant or lactating women; singleton pregnancies; absence of chronic medical illnesses	any preexisting chronic medical condition; pregestational hypertension, kidney disease, diabetes, thrombophilias; congenital fetal anomalies; multiple gestation		Private Foundation	USA; Chapel Hill, North Carolina	255/241/100	28/NR	Non-Hispanic White=71; Hispanic=62; Non-Hispanic Black=96; Race_other 1=12	Other; pregnant	controls: median 25(OH)D 98 nmol/l (IQR 68–113) cases: median 25(OH)D 75 nmol/l (IQR 47–107)

Main Analyses												
Author ,Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow -up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Baker et al., 2010	Nested Case Control	race/ethnicity	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Serum Collection	Primary-Severe Preeclampsia	25(OH)D	< 50	NR	22/160	adjusted/OR	5.41	2.02, 14.52	0.001
					25(OH)D	50–74.9	NR	10/51	adjusted/OR	2.16	0.85, 5.40	0.1
					25(OH)D	>=75	NR	11/30	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Baker et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Baker et al., 2011	Nested Case Control	Pregnant or lactating women	Type 2 DM; preeclampsia, gestational hypertension; medically indicated preterm delivery; multiple gestation; major congenital fetal anomalies; kidney disease; thrombophilias; other major chronic disease		Hospital	USA; Chapel Hill, NC	160/160/100	33/30–37	Non-Hispanic White=53; Hispanic=11; Non-Hispanic Black=33; Race_other1=5		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Baker et al., 2011	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Serum Collection	Primary-Preterm Birth	25(OH)D	<50 nmol/L	NR	3/11	adjusted/OR	0.82	0.19, 3.57	
					25(OH)D	50–74.9 nmol/L	NR	8/32	adjusted/OR	0.87	0.34, 2.25	
					25(OH)D	>=75 nmol/L	NR	29/117	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Baker et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	Y	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Barbour et al., 2012	Prospective Cohort	51–70 years; 70–79 years of age	difficulty with ADLs; cognitive impairment; inability to communicate with interviewer; intention to move; participation in other trial	Health ABC	Government	USA; Pittsburgh, PA and Memphis, TN	2640/2501/61 in lowest quartile	74.7 (2.9)/NR	Non-Hispanic Black=699	Not Reported	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532–995) 719 (517–978) 716 (501–940) Supplemental calcium intake (% yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (% yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes,

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Barbour et al., 2012	Prospective Cohort	N/R	Other Nutrients Or Dietary Factors- Serum Calcium; Anthropometrics- Estimated BMD; Medical Conditions- Estimated GFR, IL-6; Other - Time To Complete 5 Chair Stands	Primary-Hip Fracture	25(OH)D	Quartile 1: =17.78 ng/ml	2 yrs	84/2501	adjusted/HR	1.92	0.97, 3.83	0.217
					25(OH)D	Quartile 2: 17.79–24.36 ng/ml	2 yrs		adjusted/HR	0.75	0.32, 1.72	
					25(OH)D	Quartile 3: 24.37–31.94 ng/ml	2 yrs		adjusted/HR	1.86	1.00, 3.45	
					25(OH)D	Quartile 4: >31.94 ng/ml	2 yrs		adjusted/HR	1	Reference	
				Primary-Nonspine Fracture	25(OH)D	Quartile 1: =17.78 ng/ml	2 yrs	247/2494	adjusted/HR	1.21	0.83, 1.75	0.752
					25(OH)D	Quartile 2: 17.79–24.36 ng/ml	2 yrs		adjusted/HR	1.01	0.68, 1.49	
					25(OH)D	Quartile 3: 24.37–31.94 ng/ml	2 yrs		adjusted/HR	1.12	0.78, 1.60	
					25(OH)D	Quartile 4: >31.94 ng/ml	2 yrs		adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Barbour et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	Y	B	post hoc power calculation Population a) sampling random Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Barnett et al., 2010	Nested Case Control	51–70 years; men; age =65 years	inability to walk without assistance from another person.; bilateral hip replacements; inability to provide self-reported data; residence not near a study site; judged by an investigator to have a medical condition that would result in imminent death; inability to understand and sign informed consent	Osteoporotic Fractures in Men (MrOS) study	Unclear	USA; Birmingham, Alabama; Palo Alto, California; San Diego, California; Minneapolis, Minnesota; Portland, Oregon; Pittsburgh, Pennsylvania	1648/1648/0	73.6 (5.9)/NR	Non-Hispanic White=901; Hispanic=28; Non-Hispanic Black=31; Asian=27; Race_other1=13	Not Reported	25.1 ± 8.1 ng/ml in controls 25.5 ± 7.5 ng/ml in cases

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Barnett et al., 2010	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Medical Conditions- Statin Use, NSAIDs Use; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity Score For The Elderly (PASE) Score; Other - First Degree Relative With A History Of Prostate Cancer	Primary-Prostate Cancer	25(OH)D	Quartile 1(3.1–19.9ng/mL)	NR	68/411	adjusted/HR	1	reference	0.940
					25(OH)D	Quartile 2(20.0–24.9ng/mL)	NR	91/415	adjusted/HR	1.35	0.91, 2.01	
					25(OH)D	Quartile 3(25.0–29.9ng/mL)	NR	53/406	adjusted/HR	0.64	0.41, 1.00	
					25(OH)D	Quartile 4(30–75.6ng/mL)	NR	85/416	adjusted/HR	1.2	0.81, 1.78	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Barnett et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Belderbo s et al., 2011	Prospective Cohort	0–6 months; Healthy; >=37 weeks GA	Not specified		Private Foundation	Utrecht, Netherland	161/NR/44	40 weeks (GA) (0.13)/NR	Race_other1= 70; Race_other2= 30		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Belderbo s et al., 2011	Prospective Cohort	NR	Anthropometrics- Birth Weight	Primary-Respiratory Syncytial Virus Bronchiolitis	25(OH)D	<50nmol/L-NR	NR	36/NR	Adjusted/RR	6.2	1.6, 24.9	
					25(OH)D	50–74nmol/L-NR	NR	48/NR	Adjusted/RR	1.3	NR	
					25(OH)D	>=75nmol/l-NR	NR	72/NR	Adjusted/RR	1	reference	0.13

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Supplement Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Belderbos et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bodnar et al., 2010	Nested Case Control	Pregnant or lactating women; nulliparous, had no preexisting medical conditions, and delivered a live-born infant; had a maternal blood sample at <22 wk; self-identified as black or white	serum 25(OH)D concentrations were outside the detectable range		Government	USA; Pittsburgh, PA (latitude 40 degree N)	412/412/100	21/14–42	Non-Hispanic White=66; Non-Hispanic Black=34		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Bodnar et al., 2010	Nested Case Control	none	Demographics (Age, Sex, Race/Ethnicity)- SES; Anthropometrics- Prepregnancy BMI,; Smoking, Other Lifestyle Factors- Smoking During Pregnancy	Primary-Small-For-Gestational Age Births	25(OH)D	<37.5 nmol/L-white women	NR	8/11	adjusted/OR	7.5	1.8, 31.9	
					25(OH)D	37.5–75 nmol/L-white women	NR	27/134	adjusted/OR	1	Reference	
					25(OH)D	>75 nmol/L-white women	NR	42/128	adjusted/OR	2.1	1.2, 3.8	
					25(OH)D	<37.5 nmol/L-black women	NR	17/65	adjusted/OR	1.5	0.6, 3.5	
					25(OH)D	37.5–75 nmol/L-black women	NR	13/63	adjusted/OR	1	Reference	
					25(OH)D	>75 nmol/L-black women	NR	4/11	adjusted/OR	2.2	0.5, 9.0	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Bodnar et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bodnar et al., 2013	Prospective Cohort	Pregnant or lactating women; women carrying twin pregnancies; 16 weeks–20 weeks 3 days gestation	Not specified		Government	USA	211/211/100	NR/NR	Non-Hispanic White=621; Non-Hispanic Black=238; Race_other1=156		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Bodnar et al., 2013	Prospective Cohort	Not applicable	Demographics (Age, Sex, Race/Ethnicity)- Race/Ethnicity, Education; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status; Other - Parity, Marital Status, Gestational Age At Blood Sampling, 17-A(Oh)progesterone	Primary-Preterm Birth At Less Than 35 Wk	25(OH)D	< 75	24–28 weeks gestation	42/85	adjusted/OR	1	reference	
					25(OH)D	>=75	24–28 weeks gestation	33/126	adjusted/OR	0.4	0.2, 0.8	
					25(OH)D	per 1-SD increase	24–28 weeks gestation	75/211	adjusted/OR	0.5	0.3, 0.8	
					25(OH)D	Q1 (median 43.6)	24–28 weeks gestation	27/52	adjusted/OR	1	reference	
					25(OH)D	Q2 (median 72.7)	24–28 weeks gestation	24/53	adjusted/OR	1	0.4, 2.5	
					25(OH)D	Q3 (median 95.4)	24–28 weeks gestation	15/53	adjusted/OR	0.4	0.2, 1.1	
					25(OH)D	Q4 (median 116)	24–28 weeks gestation	9/53	adjusted/OR	0.2	0.1, 0.7	
				Primary-Preterm Birth At Less Than 32 Wk	25(OH)D	< 75	24–28 weeks gestation	16/85	adjusted/OR	1	reference	
					25(OH)D	>=75	24–28 weeks gestation	9/126	adjusted/OR	0.2	0.1, 0.6	
					25(OH)D	per 1-SD increase	24–28 weeks gestation	25/211	adjusted/OR	0.4	0.2, 0.8	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Q1 (median 43.6)	24–28 weeks gestation	10/52	adjusted/OR	1	reference	
					25(OH)D	Q2 (median 72.7)	24–28 weeks gestation	7/53	adjusted/OR	0.5	0.1, 1.7	
					25(OH)D	Q3 (median 95.4)	24–28 weeks gestation	6/53	adjusted/OR	0.4	0.1, 1.5	
					25(OH)D	Q4 (median 116)	24–28 weeks gestation	2/53	adjusted/OR	0.1	0.02, 0.7	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Bodnar et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Boer et al., 2012	Prospective Cohort	51–70 years; 65 years or greater; not institutionalized; expected to remain in the area** for at least 3 years	wheelchair bound in the home; receiving hospice treatment; chemotherapy; radiation therapy	Cardiovascular Health Study	Government	USA; multiple	1621/1621/70	74.0 (4.6)/NR	Non-Hispanic White=100		serum vitamin D: 66.2+/-25.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Boer et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Death	25(OH)D	Normal level	11 yrs	539/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	287/495	adjusted/HR	1.32	1.14, 1.53	
				Primary-Hip Fracture	25(OH)D	Normal level	11 yrs	118/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	72/495	adjusted/HR	1.34	0.97, 1.84	
				Primary-Cancer	25(OH)D	Normal level	11 yrs	259/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	111/495	adjusted/HR	1.13	0.90, 1.42	
				Primary-MI	25(OH)D	Normal level	11 yrs	154/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	67/495	adjusted/HR	1.24	0.91–1.70	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Boer et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bolland et al., 2010	Prospective Cohort	Postmenopausal women; Healthy; normal lumbar spine BMD; not taking agents for osteoporosis (including hormone replacement therapy or vitamin D supplements at doses >1000 IU/d); 25(OH)D ≥25 nmol/L	Not specified	ACTRN 01260500024 2628	Government	New Zealand	1471/1471/100	74 (4.2)/NR		Post menopausal	Mean seasonally adjusted 25(OH)D concentration- 50.5(17.7)nmol/L; Unadjusted mean- 50.9(19.1)nmol/L.

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Bolland et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Body Weight; Medical Conditions- Systolic Blood Pressure, And History Of Ischemic Heart Disease, Stroke Or Transient Ischemic Attack, Dyslipidemia, And Diabetes; Smoking, Other Lifestyle Factors- Smoking Status; Other - Treatment Allocation (Calcium Or Placebo)	Secondary-Death	25(OH)D2; calcium	<50 nmol/L (also took calcium)	5 yrs	21/363	adjusted/HR	1.2	0.6, 2.5	0.57
					25(OH)D2; calcium	>=50 nmol/L (also took calcium)	5 yrs	13/369	adjusted/HR	1	Reference	
					25(OH)D2	<50 nmol/L (no calcium)	5 yrs	13/373	adjusted/HR	0.9	0.4, 2.0	0.82
				Primary-MI	25(OH)D2	>=50 nmol/L (no calcium)	5 yrs	16/366	adjusted/HR	1	Reference	
					25(OH)D	<50 nmol/L	5 yrs	31/736	Adjusted/HR	1.2	0.7, 2.2	0.52
					25(OH)D	>=50 nmol/L	5 yrs	21/735	Adjusted/HR	1	Reference	
				Primary-Stroke	25(OH)D	<50 nmol/L	5 yrs	37/736	Adjusted/HR	1.4	0.8,2.5	0.20
					25(OH)D	>=50 nmol/L	5 yrs	22/735	Adjusted/HR	1	Reference	
					25(OH)D	<50 nmol/L	5 yrs	65/736	Adjusted/HR	1.2	0.8, 1.8	0.34
				Primary-MI, Stroke, Or Sudden Death	25(OH)D	<50 nmol/L	5 yrs	65/736	Adjusted/HR	1.2	0.8, 1.8	0.34
					25(OH)D	>=50 nmol/L	5 yrs	45/735	Adjusted/HR	1	Reference	
					25(OH)D	<50 nmol/L	5 yrs	24/736	Adjusted/HR	1.1	0.6, 2.0	0.76
				Primary-Tia	25(OH)D	>=50 nmol/L	5 yrs	21/735	Adjusted/HR	1	Reference	
					25(OH)D	<50 nmol/L	5 yrs	12/736	Adjusted/HR	1	0.4, 2.4	0.97
					25(OH)D	>=50 nmol/L	5 yrs	10/735	Adjusted/HR	1	Reference	
				Primary-Death	25(OH)D	<50 nmol/L	5 yrs	34/736	Adjusted/HR	0.9	0.5, 1.6	0.73
					25(OH)D	>=50 nmol/L	5 yrs	29/735	Adjusted/HR	1	1.00	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Bolland et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	Y	A	Justification of model- Y overall grade unchanged Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brandstedt et al., 2012	Nested Case Control	51–70 years; born in 1923–1945; living in Malmö, Sweden	Not specified		Private Foundation	Malmö, Sweden	1886/1842/0	61.7 (6.4)/NR		Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Brandstedt et al., 2012	Nested Case Control	age, time of blood donation	Demographics (Age, Sex, Race/Ethnicity)- Education Level; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Alcohol Consumption, Smoking	Primary-Prostate Cancer	25(OH)D	Quartile 1(<=68nmol/L)	NR	206/448	adjusted/OR	1	reference	
					25(OH)D	Quartile 2(69–84nmol/L)	NR	237/469	adjusted/OR	1.25	0.95, 1.65	
					25(OH)D	Quartile3(85–102nmol/L)	NR	245/471	adjusted/OR	1.37	1.03, 1.82	
					25(OH)D	Quartile 4(>=103nmol/L)	NR	230/454	adjusted/OR	1.34	0.99, 1.82	0.048

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Brandstedt et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brodin et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age >24 years	previous history of VTE; not officially registered inhabitants of the municipality of Tromso at baseline; missing values of serum 25(OH)D	Tromso study	Unclear	Norway	6021/5905/63	62 (10)/NR		Not Reported	mean 25(OH)D: 58.1 +/- 19.8 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Brodin et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Body Mass Index; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Total Venous Thromboembolism	25(OH)D	<=44	10.7 yrs	50/1474	adjusted/HR	1	Reference	0.89
					25(OH)D	45–56	10.7 yrs	58/1470	adjusted/HR	0.72	0.41, 1.30	
					25(OH)D	57–69	10.7 yrs	46/1481	adjusted/HR	0.93	0.55, 1.50	
					25(OH)D	>=70	10.7 yrs	47/1480	adjusted/HR	0.76	0.45, 1.28	
					25(OH)D	per 1 sd decrease in serum 25(OH)D	10.7 yrs	201/5905	adjusted/HR	1.02	0.91, 1.22	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Brodin et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brunner et al., 2011	RCT/CCT	51–70 years; Postmenopausal women; age 50–79 years	current daily use of at least 600 IU of supplemental vitamin D (single supplement and multivitamin combined) or calcitriol; history of renal calculi or hypercalcemia; predicted survival of less than 3 yr; current use of oral corticosteroids	Women's Health Initiative (WHI)	Government	Not reported	36,282/36282/ 100	NR/50–79	Non-Hispanic White=833; Hispanic=40; Non-Hispanic Black=91; Asian=19; Race_other1=04; Race_other2=12	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Brunner et al., 2011	RCT/CCT	NR	NR	Primary-Total Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	1306/18176	adjusted/HR	0.98	0.90, 1.05	0.78
						placebo	7 yrs	1333/18106	adjusted/HR	1	Reference	
				Primary-Invasive Breast Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	505/18176	adjusted/HR	0.96	0.85, 1.09	0.26
						placebo	7 yrs	523/18106	adjusted/HR	1	Reference	
				Primary-Invasive Colon Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	117/18176	adjusted/HR	0.98	0.76, 1.27	0.72
						placebo	7 yrs	118/18106	adjusted/HR	1	Reference	
				Primary-Invasive Rectal Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	41/18176	adjusted/HR	1.42	0.88, 2.28	0.16
						placebo	7 yrs	29/18106	adjusted/HR	1	Reference	
				Primary-Invasive Pancreatic Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	32/18176	adjusted/HR	0.88	0.55, 1.41	0.46
						placebo	7 yrs	36/18106	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	315/18176	adjusted/HR	0.9	0.77, 1.05	0.25
						placebo	7 yrs	347/18106	adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Brunner et al., 2011	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Burgi et al., 2011	Nested Case Control	Navy female recruits	Not specified		Government	USA	1200/1200/100	19.5 (1.8)/NR	Non-Hispanic White=54; Non-Hispanic Black=12; Race_other1=34	Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Burgi et al., 2011	Nested Case Control	age, race/ethnicity, length of military service, date of blood draw	Sun Exposure- Latitude Of Home	Primary-Stress Fracture	25(OH)D	1.5–19.7 ng/ml	NR	600/1200	adjusted/OR	1	Reference	0.02
					25(OH)D	19.8–26.6 ng/ml	NR		adjusted/OR	0.77	0.54, 1.11	
					25(OH)D	26.7–32.8 ng/ml	NR		adjusted/OR	0.76	0.52, 1.10	
					25(OH)D	32.9–39.8 ng/ml	NR		adjusted/OR	0.61	0.42, 0.91	
					25(OH)D	39.9–112.5 ng/ml	NR		adjusted/OR	0.51	0.34, 0.78	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Burgi et al., 2011	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Burns et al., 2012	RCT/CCT	expeditioners; free of disease; no use of medication known to affect bone	severe vit D deficiency (<12.5 nmol/L); serum Vit D >100 nmol/L		Trans-Antarctic Association, Private foundation: the Austin Hospital Medical Research Foundation.	Australian Antarctic Division	110/102/17	41/24–65	Non-Hispanic White=94		Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose-63+/-12 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Burns et al., 2012	RCT/CCT	NR	NR	Secondary-Femoral Neck BMD	D3 monthly (Vit D3 50,000 IU/month)		36	0.86 (sd=0.14)	final=0.85 (sd=0.13)	-0.06 (-0.12, 0)	0.06
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	0.82 (sd=0.10)	final=0.82 (sd=0.10)	-0.09 (-0.15, -0.03)	.
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	0.9 (sd=0.13)	final=0.91 (sd=0.13)		.
				Secondary-Lumbar Spine (L1-L4) BMD	D3 monthly (Vit D3 50,000 IU/month)		36	1 (sd=0.17)	final=0.98 (sd=0.16)	-0.09 (-0.17, -0.01)	0.03
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	1 (sd=0.10)	final=1.00 (sd=0.09)	-0.07 (-0.14, -0.0)	0.05
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	1.08 (sd=0.17)	final=1.07 (sd=0.18)		.
				Secondary-Total Proximal Femur BMD	D3 monthly (Vit D3 50,000 IU/month)		36	1.02 (sd=0.13)	final=0.85 (sd=0.13)	-0.23 (-0.30, -0.16)	.
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	1.01 (sd=0.08)	final=1.01 (sd=0.08)	-0.07 (-0.13, -0.01)	0.02
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	1.08 (sd=0.16)	final=1.08 (sd=0.15)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Burns et al., 2012	RCT/CCT	ND	ND	ND	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Burris et al., 2012	Prospective Cohort	Pregnant or lactating women; White or Black race; fluency in English; gestational age <22 weeks	missing both second trimester maternal plasma and cord plasma		University and hospital	USA; Massachusetts	1303/1133/100	33 (4.5)/NR	Non-Hispanic White=82; Non-Hispanic Black=18	Not Reported	

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Burris et al., 2012	Prospective Cohort	none	Demographics (Age, Sex, Race/Ethnicity)- Maternal Age, Race; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season Of Blood Draw	Secondary-Birth Weight	<25		47	NR (NR)	Final=3.46 (SD=0.68)		.
					25–50		314	NR (NR)	Final=3.55 (SD=0.52)		.
					50–75		543	NR (NR)	Final=3.53 (SD=0.51)		.
					>=75		229	NR (NR)	Final=3.51 (SD=0.52)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Burris et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Camargo et al., 2011	Prospective Cohort	0–6 months; cord blood available	Not specified		hospital	Wellington (41°S latitude) and Christchurch (43°S latitude), New Zealand	922/922/49	GA = 40 weeks (NR)/IQR: 39 – 41		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Camargo et al., 2011	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Maternal Age At Birth, New Zealand Deprivation Index, Age, Gender, Child's Ethnicity; Medical Conditions- Maternal History Of Asthma, Paternal History Of Asthma; Sun Exposure- Study Site; Smoking, Other Lifestyle Factors- Smoking During Pregnancy, Passive Smoking; Other - Endotoxin On The Bedroom Floor, Damp Musty Smell In Any Room Of Home, Duration Of Exclusive Breastfeeding	Primary-Respiratory Infection	25(OH)D	>=75nmol/L-by 3months old	NR	NR/251	Adjusted/OR	1	reference	
					25(OH)D	25-74nmol/L-by 3months old	NR	NR/491	Adjusted/OR	1.35	0.88, 2.08	
					25(OH)D	<25nmol/L-by 3months old	NR	NR/180	Adjusted/OR	2.04	1.13, 3.67	0.03
				Primary-Any Infection	25(OH)D	>=75nmol/L-by 3months old	NR	NR/251	Adjusted/OR	1	reference	
					25(OH)D	25-74nmol/L-by 3months old	NR	NR/491	Adjusted/OR	1.49	0.92, 2.43	
					25(OH)D	<25nmol/L-by 3months old	NR	NR/180	Adjusted/OR	2.36	1.17, 4.73	0.02
				Primary-Wheeze	25(OH)D	per 10nmol/L-by 15months old	NR	331/922	Adjusted/OR	0.98	0.93, 1.02	0.3
					25(OH)D	per 10nmol/L-by 3years of age	NR	472/922	Adjusted/OR	0.96	0.91, 1.00	0.04
					25(OH)D	per 10nmol/L-by 5 years of age	NR	533/922	Adjusted/OR	0.95	0.91, 0.99	0.04
				Primary-Incident Asthma	25(OH)D	per 10nmol/L-by 5 years of age	NR	181/922	Adjusted/OR	1.03	0.97, 1.10	0.02

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Camargo et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling random Outcome c) primary outcome changed to NA	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cauley et al., 2008	Nested Case Control	age, race or ethnicity, blood draw date	Other Nutrients Or Dietary Factors- Total Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Alcohol Use; Other - History Of Fracture, Oral Corticosteroid Use, Geographic Region	Primary-Hip Fractures	25(OH)D	Quartile 1: 9.2–47.5 nmol/L	7.1 yrs	NR/244	adjusted/OR	1.71	1.05, 2.79	
					25(OH)D	Quartile 2: 47.6–70.6 nmol/L	7.1 yrs	NR/195	adjusted/OR	1.09	0.70, 1.71	
					25(OH)D	Quartile 3: 60.2–70.6 nmol/L	7.1 yrs	NR/167	adjusted/OR	0.82	0.51, 1.31	
					25(OH)D	Quartile 4: 70.7–121.5 nmol/L	7.1 yrs	NR/193	adjusted/OR	1	Reference	
					25(OH)D	per 2.5 nmol/L decrease	7.1 yrs	NR/799	adjusted/OR	1.03	1.01, 1.05	0.015
					25(OH)D	per 25 nmol/L decrease	7.1 yrs	NR/799	adjusted/OR	1.33	1.06, 1.68	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cauley et al., 2008	Y	Y	Y	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cauley et al., 2011	Nested Case Control	19–50 years; 51–70 years; Postmenopausal women; aged 50–79; unlikely to move or die within 3 years; not enrolled in WHI clinical trial; not currently participating in any other clinical trial	Use of bisphosphonates, selective estrogen receptor modulators (SERMs), or tamoxifen; “other” or “unknown” race/ethnicity, current hormone therapy; missing important covariates	WHI OS	hospital and university	USA	2264/2232/100	64/50–70	Non-Hispanic White=34; Hispanic=17; Non-Hispanic Black=33; Asian=10; Race_other1=4	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cauley et al., 2011	Nested Case Control	age at screening, race/ethnicity, blood draw date	Other Nutrients Or Dietary Factors- Total Calcium Intake; Anthropometrics- Weight, Height; Medical Conditions- History Of Fracture; Smoking, Other Lifestyle Factors- Physical Activity	Primary-Fractures	25(OH)D	<20 ng/ml-whites	8.6 yrs	150/270	adjusted/OR	1	Reference	0.02
					25(OH)D	20—<30 ng/ml-whites	8.6 yrs	156/321	adjusted/OR	0.82	0.58, 1.16	
					25(OH)D	>=30 ng/ml-whites	8.6 yrs	84/189	adjusted/OR	0.56	0.35, 0.90	
					25(OH)D	<20 ng/ml-blacks	8.6 yrs	241/508	adjusted/OR	1	Reference	0.043
					25(OH)D	20—<30 ng/ml-blacks	8.6 yrs	108/193	adjusted/OR	1.48	1.05, 2.10	
					25(OH)D	>=30 ng/ml-Blacks	8.6 yrs	30/57	adjusted/OR	1.33	0.73, 2.43	
					25(OH)D	<20 ng/ml-Hispanics	8.6 yrs	89/182	adjusted/OR	1	Reference	0.72
					25(OH)D	20—<30 ng/ml-Hispanics	8.6 yrs	71/140	adjusted/OR	1.02	0.69, 1.79	
					25(OH)D	>=30 ng/ml-Hispanics	8.6 yrs	31/60	adjusted/OR	1.09	0.50, 2.37	
					25(OH)D	<20 ng/ml-Asians	8.6 yrs	37/80	adjusted/OR	1	Reference	0.22
					25(OH)D	20—<30 ng/ml-Asians	8.6 yrs	45/85	adjusted/OR	1.49	0.76, 2.93	
					25(OH)D	>=30 ng/ml-Asians	8.6 yrs	30/59	adjusted/OR	1.66	0.68, 4.02	
					25(OH)D	<20 ng/ml-native Americans	8.6 yrs	29/55	adjusted/OR	1	Reference	0.29
					25(OH)D	20—<30 ng/ml-native Americans	8.6 yrs	9/18	adjusted/OR	0.64	0.15, 2.79	
					25(OH)D	>=30 ng/ml-native Americans	8.6 yrs	6/15	adjusted/OR	0.43	0.09, 2.08	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cauley et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	WHI observational study Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cawthon et al., 2010	Prospective Cohort	51–70 years; walk without assistance, not have had bilateral hip replacement; >= 65 years old	assay problem, insufficient sample for the vitamin D assay, missing data on covariates		Government	USA	1490/1490/0	74/>=65		Other; >80% Excellent/good health status	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cawthon et al., 2010	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Serum Calcium And Phosphate; Demographics (Age, Sex, Race/Ethnicity)- Age, Race, Education; Anthropometrics- Percentage Body Fat, Weight; Medical Conditions- GFR, Health Status, Presence Of At Least One Medical Condition; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Alcohol Use, Activity Level; Other - Marital Status, And Presence Of A Functional Or Mobility Limitation	Primary-Cancer Mortality	25(OH)D	Quartile 1: <19.9 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.52	0.27, 1.00	0.086
					25(OH)D	Quartile 2: =19.9 to <25.2 ng/ml	7.3 yrs	NR/370	adjusted/HR	0.9	0.51, 1.60	
					25(OH)D	Quartile 3: =25.2 to <30.0 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.8	0.45, 1.41	
					25(OH)D	Quartile 4: =30.0	7.3 yrs	NR/376	adjusted/HR	1	reference	
					25(OH)D	Deficient, <20 ng/ml	7.3 yrs	NR/376	adjusted/HR	0.51	0.27, 0.98	0.044
					25(OH)D	Insufficient, 20 to <30 ng/ml	7.3 yrs	NR/737	adjusted/HR	0.85	0.52, 1.40	
					25(OH)D	Sufficient, =30 ng/ml	7.3 yrs	NR/377	adjusted/HR	1	reference	
					25(OH)D	per SD decrease	7.3 yrs	NR/1490	adjusted/HR	0.8	0.64, 0.99	NR
				Primary-All-Cause Mortality	25(OH)D	Quartile 1: <19.9 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.95	0.68, 1.34	0.961
					25(OH)D	Quartile 2: =19.9 to <25.2 ng/ml	7.3 yrs	NR/370	adjusted/HR	1.05	0.75, 1.47	
					25(OH)D	Quartile 3: =25.2 to <30.0 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.89	0.64, 1.24	
					25(OH)D	Quartile 4: =30.0	7.3 yrs	NR/376	adjusted/HR	1	reference	
					25(OH)D	Deficient, <20 ng/ml	7.3 yrs	NR/376	adjusted/HR	0.94	0.67, 1.32	0.706
					25(OH)D	Insufficient, 20 to <30 ng/ml	7.3 yrs	NR/737	adjusted/HR	0.97	0.72, 1.30	
					25(OH)D	Sufficient, =30 ng/ml	7.3 yrs	NR/377	adjusted/HR	1	reference	
					25(OH)D	per SD decrease	7.3 yrs		adjusted/HR	1.01	0.89, 1.14	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cawthon et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cohen et al., 2013	Prospective Cohort	19–50 years; 51–70 years; 45–84 years old	Current cardiovascular disease; measured serum concentrations of 25(OH)D at the baseline MESA examination; serum 25(OH)D concentration suggestive of high-dose vitamin D supplementation (>100 ng/ml)	MESA	Government	USA; multiple	6436/6436/53	63.3 (10.2)/NR	Non-Hispanic White=586; Hispanic=186; Non-Hispanic Black=100; Race_other1=128	Not Reported	Serum D: <20ng/ml group:14.0 (4.4) 20–29 ng/ml group-24.8 (3.8) >=30ng/ml group-37.4 (7.2) Table 1 also gives D2 and D3 levels

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cohen et al., 2013	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Vitamin D Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity, Education, Income; Anthropometrics- Body Mass Index; Medical Conditions- Diabetes, Chronic Kidney Disease; Smoking, Other Lifestyle Factors- Smoking Status; Other - Physical Activity, Systolic Blood Pressure, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, Triglyceride Cholesterol, Parathyroid Hormone, And Natural Logarithm Of C-Reactive Protein Concentrations, Use Of Antihypertensives Or Lipid - Lowering Medications, Study Site	Primary-Incident Coronary Heart Disease Events	25(OH)D	<85.92	8.5 yrs	120/2131	adjusted/HR	1.32	0.95, 1.83	
					25(OH)D	85.92–124.58	8.5 yrs	134/2224	adjusted/HR	1.2	0.91, 1.58	
					25(OH)D	>=124.58	8.5 yrs	107/2081	adjusted/HR	1	reference	0.04
					25(OH)D	per 42.96 decrement	8.5 yrs	361/6436	adjusted/HR	1.15	1.01, 1.32	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cohen et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Connor et al., 2012	Nested Case Control	51–70 years; \geq 65 years of age	Not specified		Government	USA; Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, C	1746/777/0	74 (6)/NR	Non-Hispanic White=91	Overweight/obese; Other; diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12%	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Connor et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI; Medical Conditions- Self-Rated Health Condition, Kidney Function (EGFR), And History Of Diabetes; Sun Exposure- Latitude Of Study Site; Smoking, Other Lifestyle Factors- Physical Activity (PASE), Ever Smoked, Alcohol Drinks Per Week	Primary-Nonspine Fracture	25(OH)D	Normal level	4.6 yrs	100/594	adjusted/HR	1.2	0.8, 1.8	
					25(OH)D	Low vit D	4.6 yrs	34/183	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Connor et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Daly et al., 2009	RCT/CCT	51–70 years; Healthy; Caucasian; men; age >50 years; community-living	taken calcium-vitamin D supplements in the preceding 12 months; medication use known to affect bone metabolism; participated in regular resistance training in the previous 6 months or greater than 150 min per week of weight-bearing exercise; BMI > 35 kg/m ² ; lactose intolerance; consumed more than four alcoholic beverages per day; a history of osteoporotic fracture; medical disease or medication use known to affect bone metabolism		Manufacturer	Australia; Melbourne	167/124/0	61.2 (7.5)/NR	Non-Hispanic White=100		serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Daly et al., 2009	RCT/CCT	NR	Anthropometrics- Change In Weight; Smoking, Other Lifestyle Factors- Alcohol And Saturated Fat Intake	Secondary-DBP	D3 zxa		66	69.5 (sd=10.1)	change=4.2 (2.1, 6.2)	+0.3 (-2.6, 3.2)	.
					D3 control (no additional fortified milk)		58	71 (sd=9.8)	change=3.9 (2.0, 5.8)		.
				Secondary-SBP	D3 (400 ml reduced fat milk fortified with 1000 mg calcium+800 IU Vit D)/day		66	123.7 (sd=11.7)	change=6.8 (4.2, 9.3)	+1.5 (-2.4, 5.4)	.
					D3 control (no additional fortified milk)		58	120.4 (sd=12.1)	change=5.3 (2.4, 8.2)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization (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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Daly et al., 2009	RCT/CCT	ND	ND	Y	Y	ND	Y	Y	Y	Y	A	

ligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Dam et al., 2009	Prospective Cohort	30 years or greater; ambulatory; community dwelling; Caucasian	Not specified	Rancho Bernardo study	Government	USA; Southern California	1065/656/62	74.6 (10.3)/NR	Non-Hispanic White=98		Mean serum vitamin D concentration: men- 107.6±29.2 nmol/L, women- 100.8±33.1 nmol/L	

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Dam et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Baseline Physical Activity Level, Alcohol Use	Secondary-Change In Grip Strength (Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= -0.78 (-4.76, 6.32)	+1.55 (NC)	0.22
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= -3.30 (-1.34, 7.95)	+5.63 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= -2.01 (-6.85, 2.83)	+0.32 (NC)	.
				Secondary-Change In Grip Strength (Men)	25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= -2.33 (-7.10, 2.45)	reference (reference)	.
					25(OH)D 10–90 nmol/l		114	NR (NR)	Change= -0.71 (-2.12, 3.54)	+1.63 (NC)	0.22
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= -0.64 (-3.91, 2.63)	+1.7 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= -0.37 (-2.34, 3.07)	+1.97 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= -2.34 (-5.15, 0.48)	reference (reference)	.
				Secondary-Change In Timed Up And Go (Tug)(Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= 21.92 (16.22, 27.62)	+13.79 (NC)	0.002
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= 7.37 (2.69, 12.04)	-0.76 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= 8.48 (3.48, 13.48)	+0.35 (NC)	.
				Secondary-Change In Timed Up And Go (Tug) (Men)	25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= 8.13 (3.16, 13.10)	reference (reference)	.
					25(OH)D 10–90 nmol/l		114	NR (NR)	Change= 3.36 (-1.11, 7.82)	+1.94 (NC)	0.99
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= 3.52 (-1.75, 8.79)	+2.1 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= 4.95 (0.69, 9.21)	+3.53 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= 1.42 (-3.05, 5.09)	reference (reference)	.

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-Change In Timed Chair Stands (TCS)(Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= 21.98 (16.28, 27.67)	+14.28 (NC)	0.002
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= 7.38 (2.70, 12.06)	-0.32 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= 8.51 (3.51, 13.51)	+0.81 (NC)	.
					25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= 7.70 (2.58, 12.62)	reference (reference)	.
				Secondary-Change In Timed Chair Stands (TCS)(Men)	25(OH)D 10–90 nmol/l		114	NR (NR)	Change= 3.36 (-1.11, 7.82)	+1.94 (NC)	0.99
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= 3.52 (-1.75, 8.79)	+2.1 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= 4.95 (0.69, 9.21)	+3.53 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= 1.42 (-3.05, 5.09)	reference (reference)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Dam et al., 2009	N	Y	N	N						

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	N	NA	Y	Y	N	C	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Deo et al., 2011	Prospective Cohort	65 years or greater; not institutionalized; expected to remain in the community for at least 3 years; not under active treatment for cancer	Current cardiovascular disease; inadequate serum volume; able to provide informed written consent; taking lithium; history of primary hyperparathyroidism; implausible 25(OH)D concentrations	Cardiovascular Health Study	Government	USA; multiple	2283/2283/70	74 (4)/NR	Non-Hispanic Black=14		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Deo et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race, Education; Anthropometrics- BMI; Medical Conditions- Hypertension, Diabetes Mellitus; Sun Exposure- Season, Clinic; Smoking, Other Lifestyle Factors- Physical Activity	Primary-Sudden Cardiac Death	25(OH)D	<20 ng/mL	14 yrs (median)	31/715	Adjusted/HR	1.47	0.88, 2.46	Not significant
					25(OH)D	>=20 ng/mL	14 yrs (median)	42/1568	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Deo et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	A	reconciled - grade stays B --- Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Eaton et al., 2011	Nested Case Control	51–70 years; Postmenopausal women; 50–79 years	Current cancer; medications for bone loss (including bisphosphonates, calcitonin, and parathyroid hormone); history of ulcerative colitis or crown's disease; history of surgery to remove part of the intestine; use of a special diet for malabsorption, celiac sprue or ulcerative colitis; high blood calcium; medications that contained estrogen (up to 1 y before study entry; oral and dermal forms only), androgens (including anabolic steroids, dehydroepiandrosterone, and testosterone), selective estrogen receptor modulators, antiestrogens	WHI	Government	USA; multiple	2429/2429/100	65.1 (7.6)/NR	Non-Hispanic White=780; Hispanic=51; Non-Hispanic Black=132; Asian=16; Race_other1=10; Race_other2=12		quartiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Eaton et al., 2011	Nested Case Control	age, race/ethnicity, blood draw date, clinical center	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- Waist Circumference, BMI; Medical Conditions- History Of Hypertension, Treated Diabetes, Cvd, Cancer; Sun Exposure- Month Of Blood Draw, Latitude; Smoking, Other Lifestyle Factors- Smoking Status, Weekly Alcohol Consumption, Physical Activity; Other - Breast And Colorectal Cancers, Cad-Trial Indicator, Systolic Blood Pressure	Primary-All-Cause Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.25	0.80–1.95	0.39
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.13	0.73–1.75	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.17	0.75–1.81	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	
				Primary-Cardiovascular Disease Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.27	0.81, 1.99	0.33
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.14	0.74, 1.78	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.16	0.75, 1.80	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.39	0.88, 2.19	0.11
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.22	0.79, 1.89	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.12	0.72, 1.72	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Eaton et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	A	WHI observational study Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Eliassen et al., 2011	Prospective Cohort	19–50 years; 51–70 years	Current cancer	NHSII	Government	USA; multiple	1831/1831/100	44.9 (4.4)/NR			serum vitamin D: cases 63.4±23.7nmol/L, controls- 62.4±24.0 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Eliassen et al., 2011	Prospective Cohort	age (± 2 years); menopausal status at diagnosis; month/year of collection (± 2 months); ethnicity (African-American, Asian, Hispanic, Caucasian, Other); luteal day ((date of next period-date of luteal blood draw) ± 1 day); and for each blood collection, t	Anthropometrics- BMI At Blood Collection; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Physical Activity; Other - Premenopausal, Time Of Diagnosis Relative To Blood Collection, Age At Blood Collection, Family History Of Breast Cancer, Luteal Phase Of Premenopausal Women	Primary-Breast Cancer	25(OH)D	Quartile 1(<18.4ng/mL)	NR	141/441	adjusted/RR	1	reference	
					25(OH)D	Quartile 2(18.4 to 24.6ng/m)	NR	151/456	adjusted/RR	1.05	0.79, 1.39	
					25(OH)D	Quartile 3(24.6 to <30.6ng/m)	NR	145/452	adjusted/RR	0.95	0.71, 1.29	
					25(OH)D	Quartile 4 (>=30.6ng/mL)	NR	176/482	adjusted/RR	1.2	0.88, 1.63	0.320
				Primary-Invasive Breast Cancer	25(OH)D	Quartile 1(<18.4ng/mL)	NR	95/395	adjusted/RR	1	reference	
					25(OH)D	Quartile 2(18.4 to 24.6ng/m)	NR	98/403	adjusted/RR	1.03	0.74, 1.44	
					25(OH)D	Quartile 3(24.6 to <30.6ng/m)	NR	97/404	adjusted/RR	1.01	0.72, 1.42	
					25(OH)D	Quartile 4 (>=30.6ng/mL)	NR	125/431	adjusted/RR	1.29	0.92, 1.81	0.140

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Eliassen et al., 2011	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	cases of breast cancer were reported on biennial questionnaires and confirmed by medical record review or verbal confirmation by the nurse -- - Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Engel et al., 2010	Nested Case Control	born between 1925 and 1950; French women	Not specified	French E3N cohort	Government	France	1908/1833/100	56.9 (6.4)/NR			serum vitamin D: cases- 24.4+/-10.9 ng/ml, control- 25.1+/-11.0 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Engel et al., 2010	Nested Case Control	age (±2 years), menopausal status at blood collection, age at menopause (±2 years), study center, date of blood collection (same year)	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Other - Dietary Calcium Intake	Primary-Breast Cancer	25(OH)D	<19.8 ng/mL	<=10 years	226/630	adjusted/OR	1	reference	
					25(OH)D	19.8–27ng/mL	<=10 years	198/600	adjusted/OR	0.81	0.63, 1.04	
					25(OH)D	>27ng/mL	<=10 years	191/603	adjusted/OR	0.73	0.55, 0.96	0.020

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Engel et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Fedirko et al., 2012	Nested Case Control	Not specified	Not specified	EPIC	Government	Multiple Countries	1202/1202/59.5	62.1 (7.2)/NR			by quintiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Fedirko et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age At Diagnosis, Sex; Anthropometrics- BMI; Medical Conditions- Cancer Stage, Grade Of Tumor Differentiation, Location Of Primary Tumor; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Smoking Status, Physical Activity; Other - Year Of Diagnosis	Primary-Colorectal Cancer Specific Mortality	25(OH)D	Quintile 1:<36.3	73 mos	104/242	adjusted/HR	1	Reference	0.04
					25(OH)D	Quintile 2:36.4–48.6	73 mos	85/239	adjusted/HR	0.76	0.56, 1.02	
					25(OH)D	Quintile 3:48.7–60.5	73 mos	95/241	adjusted/HR	0.93	0.69, 1.24	
					25(OH)D	Quintile 4:60.6–76.8	73 mos	78/240	adjusted/HR	0.78	0.58, 1.06	
					25(OH)D	Quintile 5:>76.8	73 mos	82/240	adjusted/HR	0.69	0.50, 0.93	
				Primary-Overall Mortality	25(OH)D	Quintile 1:<36.3	73 mos	128/242	adjusted/HR	1	Reference	<0.01
					25(OH)D	Quintile 2:36.4–48.6	73 mos	108/239	adjusted/HR	0.82	0.63, 1.07	
					25(OH)D	Quintile 3:48.7–60.5	73 mos	117/241	adjusted/HR	0.91	0.70, 1.18	
					25(OH)D	Quintile 4:60.6–76.8	73 mos	95/240	adjusted/HR	0.78	0.59, 1.03	
					25(OH)D	Quintile 5:>76.8	73 mos	93/240	adjusted/HR	0.67	0.50, 0.88	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Fedirko et al., 2012	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	Sampling was random

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Fiscella et al., 2010	Prospective Cohort	Not specified	Not specified	NHANES-III	Government		15,363/15363/ 52	43.64/NR	Non-Hispanic White=77; Hispanic=9; Non-Hispanic Black=10; Race_other1=3		serum vitamin D: 29.5 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Fiscella et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Log (Age), Sex, Race/Ethnicity; Anthropometrics- BMI Category; Medical Conditions- Self-Reported Diabetes, Cvd; Sun Exposure- Interview Month, Region; Smoking, Other Lifestyle Factors- Currently Smoking Or Not, Physical Inactivity; Other - Self-Rated Health, Systolic Blood Pressure, EGFR, Total Cholesterol, Serum Albumin, CRP, Urinary Acr	Primary- Cardiovascular Death	25(OH)D	Q1: <18 ng/mL	138,549 person years	933/15363	Adjusted/IRR	1	Reference	
					25(OH)D	Q2: 18–24.9 ng/mL	138,549 person years		Adjusted/IRR	0.71	0.54, 0.94	NR
					25(OH)D	Q3: 25–31.9 ng/mL	138,549 person years		Adjusted/IRR	0.65	0.53, 0.79	NR
					25(OH)D	Q4: >32 ng/mL	138,549 person years		Adjusted/IRR	0.79	0.62, 1.01	NR
					25(OH)D	<18 ng/mL	138,549 person years	933/15363	Adjusted/IRR	1.4	1.16, 1.69	<0.001
					25(OH)D	>=18 ng/mL	138,549 person years		Adjusted/IRR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Fiscella et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	Sampling was random

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Forman et al., 2013	RCT/CCT	19–50 years; 51–70 years; Able to participate, understand English...; 30–80 years; written and spoken English; self-identified as black; with permission from primary care doctors	Current cancer; disorders of calcium metabolism or parathyroid function; type 1 diabetes; sarcoidosis; active malignancy other than non-melanoma skin cancer; active thyroid disease; cognitive impairment; plan on traveling to a sunny region during the supplementation phase of the study		Government	USA; Boston, MA	283/283/65.4	51/44–59	Hispanic=67; Non-Hispanic Black=933		Median serum vitamin D-15.7 (10.7–23.4 IQR) ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Forman et al., 2013	RCT/CCT	NR	NR	Secondary-Diastolic Blood Pressure	D3 Vit D3 1000 IU/day		68	79.8 (se=1.3)	final=78.0 (se=1.6)	-0.9 (-5.7, 3.9)	0.71
					D3 Vit D3 2000 IU/day		73	77.6 (se=1.4)	final=76.0 (se=1.8)	-2.9 (-7.9, 2.1)	0.26
					D3 Vit D3 4000 IU/day		70	79.8 (se=1.6)	final=78.0 (se=1.6)	-0.9 (-5.7, 3.9)	0.71
					D3 placebo		72	78 (se=1.3)	final=78.9 (se=1.8)		.
				Secondary-Systolic Blood Pressure	D3 Vit D3 1000 IU/day		68	124.7 (se=2.1)	final=122.5 (se=2.0)	-2.4 (-8.6, 3.8)	0.45
					D3 Vit D3 2000 IU/day		73	122.8 (se=2.0)	final=120.0 (se=2.4)	-4.9 (-11.6, 1.8)	0.15
					D3 Vit D3 4000 IU/day		70	130.4 (se=2.4)	final=126.6 (se=2.6)	+1.7 (-5.3, 8.7)	0.63
					D3 placebo		72	122.2 (se=2.2)	final=124.9 (se=2.4)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Forman et al., 2013	RCT/CCT	Y	ND	Y	ND	Y	ND	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Formiga et al., 2014	Prospective Cohort	community dwelling adults born in 1924	Not specified	Octabaix	Unclear	Spain	312/312/60.6	85 (0)/NR		Other; Oldest old	70 ± 75 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Formiga et al., 2014	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Sex, Educational Level, Marital Status; Medical Conditions- Charlton Index; Other - Barthel Index (Physical Performance), MEC (Cognitive Performance)	Primary-Total Mortality	25(OH)D	Q1: <34.94	2.8 yrs	15/71	unadjusted/HR	1.28	0.61, 2.6	0.41
					25(OH)D	Q2: 34.94–61.65	2.8 yrs	18/77	unadjusted/HR	1.36	0.67, 2.74	
					25(OH)D	Q3: 61.66–83.37	2.8 yrs	11/84	unadjusted/HR	0.76	0.34, 1.68	
					25(OH)D	Q4:>83.37	2.8 yrs	14/80	unadjusted/HR	1	Reference	
				Primary-Cardiovascular Mortality	25(OH)D	Q1: <34.94	2.8 yrs	6/71	unadjusted/HR	1.04	0.33, 3.24	0.86
					25(OH)D	Q2: 34.94–61.65	2.8 yrs	6/77	unadjusted/HR	0.89	0.28, 2.80	
					25(OH)D	Q3: 61.66–83.37	2.8 yrs	6/84	unadjusted/HR	1.47	0.45, 4.58	
					25(OH)D	Q4:>83.37	2.8 yrs	7/80	unadjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Formiga et al., 2014	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Freedman et al., 2010	Prospective Cohort	19–50 years; 51–70 years; 17 years and older; completed MEC exam	no 25(OH)D; unknown mortality status	NHANES-III	Government	USA; multiple	16,819/NR/12.2	44.5/NR	Non-Hispanic White=5; Hispanic=124; Non-Hispanic Black=338; Race_other1=144		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Freedman et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Sun Exposure- Season/ Latitude; Smoking, Other Lifestyle Factors- Smoking History	Primary-Total Cancer Mortality	25(OH)D	< 37.5 nmol/L-men and women, all seasons	13.4 yrs	116/NR	adjusted/RR	1	Reference	0.43
					25(OH)D	37.5—<50 nmol/L-men and women, all seasons	13.4 yrs	174/NR	adjusted/RR	1.04	0.77, 1.41	
					25(OH)D	50 —<62.5 nmol/L-men and women, all seasons	13.4 yrs	165/NR	adjusted/RR	1.23	0.89, 1.69	
					25(OH)D	62.5—80 nmol/L-men and women, all seasons	13.4 yrs	200/NR	adjusted/RR	1.19	0.86, 1.65	
					25(OH)D	80—<100 nmol/L-men and women, all seasons	13.4 yrs	139/NR	adjusted/RR	1.12	0.80, 1.57	
					25(OH)D	>=100 nmol/L-men and women, all seasons	13.4 yrs	90/NR	adjusted/RR	1.15	0.79, 1.68	
					25(OH)D	< 37.5 nmol/L-men & women, winter/lower latitude	13.4 yrs	55/NR	adjusted/RR	1	Reference	0.23
					25(OH)D	37.5—<50 nmol/L-men & women, winter/lower latitude	13.4 yrs	79/NR	adjusted/RR	1.3	0.77, 2.19	
					25(OH)D	50 —<62.5 nmol/L-men & women, winter/lower latitude	13.4 yrs	57/NR	adjusted/RR	1.2	0.64, 2.26	
					25(OH)D	62.5—80 nmol/L-men & women, winter/lower latitude	13.4 yrs	78/NR	adjusted/RR	1.67	0.98, 2.86	
					25(OH)D	80—<100 nmol/L-men & women, winter/lower latitude	13.4 yrs	54/NR	adjusted/RR	1.31	0.77, 2.23	
					25(OH)D	>=100 nmol/L-men & women, winter/lower latitude	13.4 yrs	32/NR	adjusted/RR	1.5	0.74, 3.02	
					25(OH)D	< 37.5 nmol/L-men & women, summer/higher latitude	13.4 yrs	61/NR	adjusted/RR	1	Reference	0.67
					25(OH)D	37.5—<50 nmol/L-men & women, summer/higher latitude	13.4 yrs	95/NR	adjusted/RR	0.91	0.63, 1.32	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	50 —<62.5 nmol/L-men & women, summer/higher latitude	13.4 yrs	108/NR	adjusted/RR	1.19	0.78, 1.82	
					25(OH)D	62.5–80 nmol/L-men & women, summer/higher latitude	13.4 yrs	122/NR	adjusted/RR	1.02	0.67, 1.54	
					25(OH)D	80—<100 nmol/L-men & women, summer/higher latitude	13.4 yrs	85/NR	adjusted/RR	1.03	0.66, 1.63	
					25(OH)D	>=100 nmol/L-men & women, summer/higher latitude	13.4 yrs	58/NR	adjusted/RR	1.02	0.63, 1.45	
					25(OH)D	< 37.5 nmol/L-men, all seasons	13.4 yrs	47/NR	adjusted/RR	1	Reference	0.09
					25(OH)D	37.5—<50 nmol/L-men, all seasons	13.4 yrs	95/NR	adjusted/RR	1.66	0.98, 2.80	
					25(OH)D	50 —<62.5 nmol/L-men, all seasons	13.4 yrs	90/NR	adjusted/RR	1.43	0.90, 2.26	
					25(OH)D	62.5–80 nmol/L-men, all seasons	13.4 yrs	122/NR	adjusted/RR	1.52	0.82, 2.80	
					25(OH)D	80—<100 nmol/L-men, all seasons	13.4 yrs	90/NR	adjusted/RR	1.66	1.06, 2.61	
					25(OH)D	>=100 nmol/L-men, all seasons	13.4 yrs	69/NR	adjusted/RR	1.85	1.02, 3.35	
					25(OH)D	< 37.5 nmol/L-men, winter/lower latitude	13.4 yrs	25/NR	adjusted/RR	1	Reference	0.55
					25(OH)D	37.5—<50 nmol/L-men, winter/lower latitude	13.4 yrs	51/NR	adjusted/RR	2.58	1.37, 4.87	
					25(OH)D	50 —<62.5 nmol/L-men, winter/lower latitude	13.4 yrs	31/NR	adjusted/RR	1.14	0.48, 2.70	
					25(OH)D	62.5–80 nmol/L-men, winter/lower latitude	13.4 yrs	52/NR	adjusted/RR	1.99	0.86, 4.13	
					25(OH)D	80—<100 nmol/L-men, winter/lower latitude	13.4 yrs	33/NR	adjusted/RR	1.42	0.74, 2.72	
					25(OH)D	>=100 nmol/L-men, winter/lower latitude	13.4 yrs	23/NR	adjusted/RR	1.94	0.69, 5.45	
					25(OH)D	< 37.5 nmol/L-men, summer/higher latitude	13.4 yrs	22/NR	adjusted/RR	1	Reference	0.045

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	37.5–<50 nmol/L-men, summer/higher latitude	13.4 yrs	44/NR	adjusted/RR	1.28	0.51, 3.23	
					25(OH)D	50 –<62.5 nmol/L-men, summer/higher latitude	13.4 yrs	59/NR	adjusted/RR	1.55	0.81, 2.99	
					25(OH)D	62.5–80 nmol/L-men, summer/higher latitude	13.4 yrs	70/NR	adjusted/RR	1.33	0.53, 3.53	
					25(OH)D	80–<100 nmol/L-men, summer/higher latitude	13.4 yrs	57/NR	adjusted/RR	1.76	0.87, 3.57	
					25(OH)D	>=100 nmol/L-men, summer/higher latitude	13.4 yrs	46/NR	adjusted/RR	1.84	0.85, 3.98	
					25(OH)D	< 37.5 nmol/L-women, all seasons	13.4 yrs	69/NR	adjusted/RR	1	Reference	0.29
					25(OH)D	37.5–<50 nmol/L-women, all seasons	13.4 yrs	79/NR	adjusted/RR	0.85	0.59, 1.22	
					25(OH)D	50 –<62.5 nmol/L-women, all seasons	13.4 yrs	75/NR	adjusted/RR	1.25	0.82, 1.90	
					25(OH)D	62.5–80 nmol/L-women, all seasons	13.4 yrs	78/NR	adjusted/RR	1.11	0.69, 1.79	
					25(OH)D	80–<100 nmol/L-women, all seasons	13.4 yrs	49/NR	adjusted/RR	0.86	0.50, 1.46	
					25(OH)D	>=100 nmol/L-women, all seasons	13.4 yrs	21/NR	adjusted/RR	0.64	0.35, 1.18	
					25(OH)D	< 37.5 nmol/L-women, winter/lower latitude	13.4 yrs	30/NR	adjusted/RR	1	Reference	0.42
					25(OH)D	37.5–<50 nmol/L-women, winter/lower latitude	13.4 yrs	28/NR	adjusted/RR	0.74	0.36, 1.51	
					25(OH)D	50 –<62.5 nmol/L-women, winter/lower latitude	13.4 yrs	26/NR	adjusted/RR	1.27	0.51, 3.18	
					25(OH)D	62.5–80 nmol/L-women, winter/lower latitude	13.4 yrs	26/NR	adjusted/RR	1.44	0.61, 3.38	
					25(OH)D	80–<100 nmol/L-women, winter/lower latitude	13.4 yrs	21/NR	adjusted/RR	1.28	0.50, 3.24	
					25(OH)D	>=100 nmol/L-women, winter/lower latitude	13.4 yrs	9/NR	adjusted/RR	1.01	0.26, 3.90	
					25(OH)D	< 37.5 nmol/L-women, summer/higher latitude	13.4 yrs	39/NR	adjusted/RR	1	Reference	0.03
					25(OH)D	37.5–<50 nmol/L-women, summer/higher latitude	13.4 yrs	51/NR	adjusted/RR	0.88	0.54, 1.43	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	50 —<62.5 nmol/L-women, summer/higher latitude	13.4 yrs	49/NR	adjusted/RR	1.18	0.65, 2.12	
					25(OH)D	62.5–80 nmol/L-women, summer/higher latitude	13.4 yrs	52/NR	adjusted/RR	0.99	0.52, 1.87	
					25(OH)D	80—<100 nmol/L-women, summer/higher latitude	13.4 yrs	28/NR	adjusted/RR	0.7	0.34, 1.44	
					25(OH)D	>=100 nmol/L-women, summer/higher latitude	13.4 yrs	12/NR	adjusted/RR	0.52	0.25, 1.10	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Freedman et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ganmaa et al., 2012	RCT/CCT	9–18 years; 12–15 years; residing in Ulaanbaatar	Not specified		Manufacturer	China ;Ulaanbaatar, Mongolia	120/117/47.5	13.1 (1.5)/NR		Other; latent tuberculosis	18+/-10 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Ganmaa et al., 2012	RCT/CCT	NR	NR	Primary-Tuberculin Skin Test(Tst)	Vit D	800IU/day-NR	NR	17/59	Adjusted/RR	0.41	0.16, 1.09	0.06
					Vit D	Placebo-NR	NR	24/58	Adjusted/RR	1	reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Ganmaa et al., 2012	RCT/CCT	Y	Y	ND	Y	Y	N	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Gepner et al., 2012	RCT/CCT	Postmenopausal women; Healthy; serum 25(OH)D concentrations between 10–60ng/ml; community dwelling; ambulatory	use of medications that interfere with vitamin D metabolism or affect bone turn over; active metabolites of vitamin D within 6 months of screening; history of CVD; serum calcium >10.5mg/dl; untreated hyperparathyroidism; history of nephrolithiasis, hypercalciuria, malignancy, tuberculosis, sarcoidosis; Paget's disease; malabsorption syndromes; estimated glomerular filtration rate<=25 mL/minute; use of tanning beds or salons, unwilling to use sunscreen during periods of sun exposure >15 minutes		university	USA; Madison, WI	114/114/100	63.9 (3.0)/NR		Post menopausal	serum vitamin D- 31.3+/- 10.6 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Gepner et al., 2012	RCT/CCT	NR	Anthropometrics- BMI	Secondary-Brachial DBP	D3 placebo		57	72.6 (sd=7.1)	change=-0.4 (sd=4.4)		.
					D3 Vit D3 2500 IU/day		57	72.45 (sd=7.6)	change=-0.7 (sd=5.1)	-0.3 (-2.1, 1.5)	0.73
				Secondary-Brachial SBP	D3 placebo		57	122.2 (sd=11.8)	change=-2.5 (sd=10.9)		.
					D3 Vit D3 2500 IU/day		57	122.3 (sd=13.1)	change=-0.3 (sd=8.4)	+2.2 (-1.4, 5.8)	0.23
				Secondary-Central DBP	D3 placebo		57	73.7 (sd=7.1)	change=-0.5 (sd=4.4)		.
					D3 Vit D3 2500 IU/day		57	73.5 (sd=7.7)	change=-0.7 (sd=5.1)	-0.2 (-2.0, 1.6)	0.82
				Secondary-Central SBP	D3 placebo		57	115.6 (sd=11.1)	change=-2.1 (sd=9.7)		.
					D3 Vit D3 2500 IU/day		57	116.7 (sd=12.2)	change=-0.3 (sd=7.0)	+1.8 (-1.3, 4.9)	0.26

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Gepner et al., 2012	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Gernand et al., 2013	Prospective Cohort	Pregnant or lactating women; singleton gestation; white, black or Puerto Rican maternal race/ethnicity; entry to prenatal care at 26 weeks or less; available stored serum sample at 26 weeks or less	Hypertension; Type 2 DM; diabetes; stillbirth; preterm birth; serum unsuitable for vitamin d measurement; missing covariates	Collaborative Perinatal Project	Government	USA; multiple	2146/2146/100	NR/NR	Non-Hispanic White=521; Hispanic=63; Non-Hispanic Black=416	Other; pregnant	maternal serum vitamin D: 51.3+/-28.0 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Gernand et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Maternal Race/Ethnicity; Anthropometrics- Prepregnancy BMI, Height; Sun Exposure- Season And Study Site; Smoking, Other Lifestyle Factors- Smoking	Secondary-Birth Weight	<37.5		747	NR (NR)	Final=3127 (SD=15)		.
					>=37.5		1399	NR (NR)	Final=3215 (SD=11)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Gernand et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ginde et al., 2009	Prospective Cohort	>= 65 years; Non-institutionalized US civilian population	Not specified	NHANES III	Government	USA; multiple	3408/3408/56	73 (0.2)/NR	Non-Hispanic White=87; Hispanic=2; Non-Hispanic Black=7; Race_other1=4		median 25(OH) D level- 66.0 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Ginde et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Medical Conditions- Asthma, Copd, Hypertension, Diabetes, Hyperlipidemia; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Physical Activity, Smoking Status, Cigarette Pack Years; Other - Region, Renal Function, History Of MI, Stroke, Cancer (Nonskin)	Secondary- Cardiovascular Death	25(OH)D	<25.0 nmol/L	7.3 yrs	767/115	Adjusted/HR	2.36	1.17, 4.75	<0.05
					25(OH)D	25.0–49.9 nmol/L	7.3 yrs	NR/904	Adjusted/HR	1.54	1.01, 2.34	<0.05
					25(OH)D	50.0–74.9 nmol/L	7.3 yrs	NR/1296	Adjusted/HR	1.26	0.85, 1.88	NS
					25(OH)D	75.0–99.9 nmol/L	7.3 yrs	NR/775	Adjusted/HR	1.2	0.79, 1.81	NS
					25(OH)D	>=100.0 nmol/L	7.3 yrs	NR/318	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Ginde et al., 2009	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Goldring et al., 2013	RCT/CCT	0–6 months; 7 months–2 years; 3–8 years; children 0–3 years of age; mothers participated in vitamin D RCT from 27 weeks gestation; black, white, Asian or middle eastern	known sarcoidosis, osteomalacia, renal dysfunction, tuberculosis		Private Foundation	UK	180/106/56	3/NR	Non-Hispanic White=26; Non-Hispanic Black=24; Asian=24; Race_other1=26	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Goldring et al., 2013	RCT/CCT	Not applicable	Other Nutrients Or Dietary Factors- Vitamin Supplementation; Demographics (Age, Sex, Race/Ethnicity)- Maternal Ethnicity, Maternal Education; Smoking, Other Lifestyle Factors- Smokers In Household, Maternal Smoking During Pregnancy; Other - Family History Of Allergy, Number Of Children In Household, Baseline Maternal 25(Oh)d	Primary-Wheeze Ever	D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	3 yrs	11/56	adjusted/OR	0.56	0.20, 1.57	0.27
						control	3 yrs	14/50	adjusted/OR	1	reference	
				Secondary-Lower Respiratory Tract Infection	D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	3 yrs	14/54	adjusted/OR	1	0.35, 2.91	1
						control	3 yrs	11/50	adjusted/OR	1	reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Goldring et al., 2013	RCT/CCT	Y	Y	NA	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Green et al., 2010	Nested Case Control	Postmenopausal women; nurses; no history of cancer at the time of blood sample	Not specified	Nurses' Health Study	Government	USA; multiple	960/469/100	61.0/NR		Post menopausal	tertiles	

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Green et al., 2010	Nested Case Control	age +/- 2years, fasting status at the time of blood collection, and PMH use, month of blood collection, time of day that blood was drawn (62 hr)	Demographics (Age, Sex, Race/Ethnicity)- Age At Mammography; Smoking, Other Lifestyle Factors- Alcohol Intake, Smoking Status; Other - Personal History Of Benign Breast Disease, Age At Menarche, Parity, Age At First Birth, Use Of Postmenopausal Hormones, Age At Menopause	Secondary-Percent Mammographic Density	1,25(OH)2D: 1st quartile (13.0–29.1 ng/ml)		110	NR (NR)	final=25.5 (NR)		.
					1,25(OH)2D: 2nd quartile (29.2–33.1 ng/ml)		108	NR (NR)	final=27.6 (NR)	+2.1 (NC)	.
					1,25(OH)2D: 3rd quartile (33.2–37.3 ng/ml)		110	NR (NR)	final=23.3 (NR)	-2.2 (NC)	.
					1,25(OH)2D: 4th quartile (37.4–56.2 ng/ml)		114	NR (NR)	final=25.8 (NR)	+0.3 (NC)	.
					25(OH)D: 1st quartile (cut points vary by batches)		118	NR (NR)	final=26.3 (NR)		.
					25(OH)D: 2nd quartile		115	NR (NR)	final=25.6 (NR)	-0.7 (NC)	.
					25(OH)D: 3rd quartile		124	NR (NR)	final=24.8 (NR)	-1.5 (NC)	.
					25(OH)D: 4th quartile		112	NR (NR)	final=25.7 (NR)	-0.6 (NC)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Green et al., 2010	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	medical record reviews were used to confirm breast cancer diagnoses but article did not state whether diagnoses were verified independently Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Grimnes et al., 2012	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–80 years; T-score in total hip or lumbar spine (L2–4)=−2.0	Current cancer; Current cardiovascular disease; Type 2 DM; hormone replacement therapy or other therapy affecting bone remodeling during the last 12 months before enrollment; use of steroids; renal stone disease; systolic blood pressure >175mmHg or diastolic blood pressure >105mmHg; serum creatinine >110 μmol/l; suspected hyperparathyroidism; chronic disease like ischemic heart disease, diabetes, granulomatous disease, and cancer		Manufacturer	Norway	297/297/100	63.5 (6.8)/NR		Post menopausal	serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Grimnes et al., 2012	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Sun Exposure- Reported Outdoor Time, Sunny Holidays, Sun Bed Use; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Secondary-Total Hip BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.79 (sd=0.073)	change=0.31 (sd=1.59)	-0.25 (-0.63, 0.13)	0.19
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.791 (sd=0.082)	change=0.56 (sd=1.70)		.
				Secondary-Femoral Neck BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.758 (sd=0.066)	change=0.03 (sd=2.08)	-0.14 (-0.59, 0.31)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.757 (sd=0.079)	change=0.17 (sd=1.87)		.
				Secondary-L2-L4 BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.901 (sd=0.072)	change=0.25 (sd=3.19)	-0.07 (-0.80, 0.66)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.902 (sd=0.079)	change=0.32 (sd=3.23)		.
				Secondary-Total Body BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	1 (sd=0.054)	change=0.18 (sd=1.14)	-0.02 (-0.29, 0.25)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	1.002 (sd=0.055)	change=0.20 (sd=1.23)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Grimnes et al., 2012	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Holland et al., 2012	RCT/CCT	0–6 months; 7 months–2 years; infants aged 1–11 months; living within the socioeconomically deprived study districts	vitamin D within previous 3 months; families expecting to move to another town within 18 months; rickets; clinical diagnosis of Kwashiorkor or Marasmus		Private Foundation	Kabul, Afghanistan	3046/NR/48	NR/NR		Malnourished/frailty	only box plot of figure 3

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Holland et al., 2012	RCT/CCT	NR	NR	Primary-All Pneumonia First Episode	Vit D3	100,000IU-confirmed chest radiograph confirmed	NR	260/NR	Adjusted/IRR	1.065	0.895, 1.268	0.476
						Placebo-confirmed chest radiograph confirmed	NR	2445/NR	Adjusted/IRR	1	reference	
				Primary-All Pneumonia Repeat Episode	Vit D3	100,000IU-confirmed chest radiograph confirmed	NR	138/NR	Adjusted/IRR	1.685	1.282, 2.212	<0.0001
						Placebo-confirmed chest radiograph confirmed	NR	82/NR	Adjusted/IRR	1	reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Holland et al., 2012	RCT/CCT	Y	ND	Y	N	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hollis et al., 2011	RCT/CCT	Pregnant or lactating women; maternal age of 16 years or greater at the time of consent; confirmed singleton pregnancy of fewer than 16 completed weeks of gestation at the time of consent; planned to receive ongoing prenatal care in the Charleston, SC, area.; ability to provide written informed consent at the first visit.	required chronic diuretic or cardiac medication therapy, including calcium channel blockers; suffered chronic hypertension; Pregnant women with preexisting calcium or parathyroid conditions; Women with a pregnancy at greater than 16 weeks of gestation as calculated by their last menstrual period; active thyroid disease		Government	USA; Charleston, SC	502/350/100	27.0 (5.6)/18–41	Non-Hispanic White=342; Hispanic=405; Non-Hispanic Black=252		serum: delivered group- 59.5.8 nmol/L (6.0–172.5) exited group- 50.5.1nmol/L (6.5–120.5) vit D intake: 400 IU group- 181.6+/-108.4 IU/d, 2000 IU group- 195.8+/-135.0, 4000 IU group- 204.2+/-148.2 calcium intake: 400 IU group-1063.6+/-539.6 mg

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Hollis et al., 2011	RCT/CCT	NR	NR	Secondary-Birth Weight	Vit D 4000 IU		117	NR (NR)	Final=3284.6 (3175.2, 3394.0)	+62.8 (-103.4, 229.0)	0.23
					Vit D 2000 IU		122	NR (NR)	Final=3360.1 (3255.2, 3465.0)	+138.3 (-24.4, 301.0)	.
					Vit D 400 IU		111	NR (NR)	Final=3221.8 (3094.9, 3348.8)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Hollis et al., 2011	RCT/CCT	Y	ND	ND	N	ND	N	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Holvik et al., 2013	Prospective Cohort	51–70 years; age 65–79 years; home-dwelling	Not specified	Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)	Government	Norway	21774/1022/72	71.9 (3.9)/NR		Other; 46.1–59.2% good or very good health	median (25th and 75th percentiles) s-25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Holvik et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Sun Exposure- Month Of Blood Sample	Primary-Hip Fracture	25(OH)D	Q1: 4.5–42.1	10.7 yrs	317/256	adjusted/HR	1.34	1.05, 1.70	
					25(OH)D	Q2: 42.2–53.5	10.7 yrs	294/255	adjusted/HR	1.13	0.90, 1.44	
					25(OH)D	Q3: 53.5–67.8	10.7 yrs	272/255	adjusted/HR	1.1	0.87, 1.39	
					25(OH)D	Q4: 67.9–250.0	10.7 yrs	279/256	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Holvik et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	Y	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hosseinp anah et al., 2011	Nested Case Control	19–50 years; 51–70 years; Healthy; free of CVD and kidney disease; age >30	Not specified	Tehran Lipid and Glucose Study (TLGS)	Unclear	Tehran, Iran	502/502/48.6	56.84 (11.17)/NR			25-OH-D concentration (ng/ml): cases- 12.5 (8.4- 24.4); controls 18.1(11–31)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Hosseinp anah et al., 2011	Nested Case Control	age, sex, month of study entry, length of follow up	Anthropometrics- BMI; Medical Conditions- Diabetes Mellitus, Hypertension, Hypercholesterolemia, Hypertriglyceridemia, Low HDL	Primary- Cardiovascular Disease	25(OH)D	<10 ng/mL	5.7 yrs	85/133	Adjusted/OR	2.9	1.76, 4.67	<0.001
					25(OH)D	10–14.99 ng/mL	5.7 yrs	86/173	Adjusted/OR	1.46	0.83, 2.56	0.18
					25(OH)D	>=15ng/mL	5.7 yrs	80/196	Adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Hosseinp anah et al., 2011	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Houston et al., 2012	Prospective Cohort	70–79 years; black and white; no difficulty walking 1/4 mile, up 10 steps, or performing basic ADLs; free of life-threatening illness	lacked 25(OH)D measurements; missing data on pertinent covariates; lacked follow-up visits at year 4 or 6	Health, Aging and Body Composition	Government	USA; Pittsburgh, Memphis	2307/1971/51.1	74.7 (2.9)/NR	Non-Hispanic White=615; Non-Hispanic Black=385	Other; diabetes, cvd, copd, knee pain	1/3- 25(OH)D <50nmol/L, 2/3—<75nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Houston et al., 2012	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin And Vitamin D-Containing Supplement Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Gender, Race, education; Anthropometrics- BMI; Medical Conditions- Kidney Function, Cognitive Function, Depressive Symptoms, Diabetes Mellitus, Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, Knee Pain; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status, Alcohol Consumption, Physical Activity; Other - Prior Hospitalization	Secondary-Knee Extensor Strength	25(OH)D <50 nmol/L		1818	12.83 (SE=0.27)	Final=11.9 (SE=0.2)	NC (NC)	0.76
					25(OH)D 50–<75 nmol/L			13.01 (SE=0.27)	Final=11.9 (SE=0.2)	NC (NC)	.
					25(OH)D ≥75 nmol/L			12.91 (SE=0.27)	Final=11.8 (SE=0.2)	NC (NC)	.
				Secondary-Grip Strength	25(OH)D <50 nmol/L		1971	28.87 (SE=0.51)	Final=29.2 (SE=0.4)	NC (NC)	0.09
					25(OH)D 50–<75 nmol/L			29.71 (SE=0.50)	Final=29.8 (SE=0.4)	NC (NC)	.
					25(OH)D ≥75 nmol/L			29.81 (SE=0.50)	Final=30.0 (SE=0.4)	NC (NC)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Houston et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hutchinson et al., 2010	Prospective Cohort	19–50 years; 51–70 years; 25–84	Not specified	Tromso	Government	Tromso, Norway	7161/7161/59.8	58.9 (10.2)/NR			Mean 25(OH)D level in the total non-smoking population -52.3 +/-16.5, men- 53.5+/-16.0 and women- 51.5 +/-16.8 nmol/l (P<0.001). Mean 25(OH)D level for smokers was 72.0G+/-0.1, men- 70.5+/-19.0 and women- 73.0+/-20.7 nmol/l (P=0.002).

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Hutchinson et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Medical Conditions- Hypertension, Prior Cvd, Diabetes, Prior Cancer; Smoking, Other Lifestyle Factors- Smoking; Other - Creatinine	Primary-All-Cause Death	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	247/1184	adjusted/HR	1.32	1.07–1.62	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	198/1187	adjusted/HR	1.06	0.86–1.31	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	190/1192	adjusted/HR	1.09	0.88–1.34	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	163/1188	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	156/597	adjusted/HR	1.06	0.83–1.35	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	143/606	adjusted/HR	0.97	0.76–1.25	
				Primary-Cvd Mortality	25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	138/607	adjusted/HR	1.04	0.81–1.33	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	124/600	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	106/1184	adjusted/HR	1.08	0.79–1.48	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	81/1187	adjusted/HR	0.84	0.61–1.15	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	62/1192	adjusted/HR	0.71	0.51–1.01	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	76/1188	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	45/597	adjusted/HR	0.93	0.61–1.44	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	57/606	adjusted/HR	1.1	0.73–1.67	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	46/607	adjusted/HR	1.04	0.67–1.60	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	40/600	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	72/1184	adjusted/HR	1.14	0.80–1.63	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	69/1187	adjusted/HR	1.13	0.80–1.61	NR
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	74/1192	adjusted/HR	1.23	0.87–1.75	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	58/1188	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	55/597	adjusted/HR	0.82	0.56–1.21	
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	54/606	adjusted/HR	0.86	0.59–1.26	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	60/607	adjusted/HR	1.02	0.70–1.48	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	56/600	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Hutchinson et al., 2010	N	Y	N	Y						N

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Islam et al., 2010	RCT/CCT	9–18 years; 19–50 years; 18–36 years; no history of serious medical conditions; residing in the city for at least 2 years; no history of medication known to affect bone metabolism	Not specified		Manufacturer	Dhaka, Bangladesh	200/116/100	22.9 (3.9)/NR			placebo-35.0 +/-9.4 nmol/L Vit D-37.1+/-12.1 nmol/L VitD+Ca- 37.8+/-10.9 nmol/L MMN+D+Ca- 36.9+/-12.5 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Islam et al., 2010	RCT/CCT	NR	NR	Secondary-Femoral Neck BMC	D VD (Vit D 10 µg)/day		40	3.384 (sd=0.660)	change=0.061 (sd=0.205)	+0.14 (0.05, 0.22)	.
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	3.436 (sd=0.551)	change=0.069 (sd=0.174)	+0.14 (0.07, 0.22)	.
					D Placebo		35	3.316 (sd=0.533)	change=-0.075 (sd=0.146)		.
				Secondary-Femoral Neck BMD	D VD (Vit D 10 µg)/day		40	0.8 (sd=0.118)	change=0.012 (sd=0.028)	+0.02 (0.01, 0.03)	.
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.799 (sd=0.120)	change=0.013 (sd=0.030)	+0.02 (0.01, 0.03)	.
					D Placebo		35	0.768 (sd=0.967)	change=-0.010 (sd=0.012)		.
				Secondary-Lumbar Spine L2-L4 BMC	D VD (Vit D 10 µg)/day		40	32.548 (sd=4.845)	change=0.620 (sd=2.442)	+0.58 (-0.84, 2.00)	0.42
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	31.782 (sd=5.469)	change=0.687 (sd=2.761)	+0.65 (-0.82, 2.12)	0.39
					D Placebo		35	32.399 (sd=4.853)	change=0.042 (sd=3.673)		.
				Secondary-Lumbar Spine L2-L4 BMD	D VD (Vit D 10 µg)/day		40	0.898 (sd=0.113)	change=0.013 (sd=0.036)	+0.02 (-0, 0.04)	0.12
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.895 (sd=0.138)	change=0.010 (sd=0.042)	+0.01 (-0.01, 0.03)	0.22
					D Placebo		35	0.891 (sd=0.101)	change=-0.003 (sd=0.049)		.
				Secondary-Trochanter BMC	D VD (Vit D 10 µg)/day		40	5.818 (sd=1.289)	change=0.158 (sd=0.549)	+0.31 (0.09, 0.53)	0.01
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	5.877 (sd=1.335)	change=0.090 (sd=0.419)	+0.24 (0.06, 0.43)	0.01
					D Placebo		35	5.885 (sd=1.125)	change=-0.151 (sd=0.389)		.
				Secondary-Trochanter BMD	D VD (Vit D 10 µg)/day		40	0.634 (sd=0.097)	change=0.002 (sd=0.021)	+0.02 (0.01, 0.03)	0.002
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.625 (sd=0.105)	change=0.001 (sd=0.026)	+0.02 (0.01, 0.03)	0.01
					D Placebo		35	0.619 (sd=0.082)	change=-0.017 (sd=0.029)		.
				Secondary-Ward's Triangle BMD	D VD (Vit D 10 µg)/day		40	0.654 (sd=0.131)	change=0.010 (sd=0.035)	+0.03 (0.01, 0.04)	.

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.654 (sd=0.132)	change=0.015 (sd=0.031)	+0.03 (0.02, 0.05)	.
					D Placebo		35	0.628 (sd=0.108)	change=-0.018 (sd=0.027)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Islam et al., 2010	RCT/CCT	Y	ND	ND	Y	Y	ND	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jackson et al., 2011	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–79 years; not likely to change residence; no evidence of a medical condition associated with predicted survival of less than 3 years at the time of enrollment	Not specified	WHI	Government	USA; multiple	1970/1528/100	NR/NR	Non-Hispanic White=828; Hispanic=42; Non-Hispanic Black=119; Asian=0; Race_other1=08; Race_other2=03	Post menopausal	vitamin D intake: placebo- 7.54+/-6.36 ug/d, CaD- 7.42+/-5.84 ug/d calcium intake: placebo- 1049+/- 625.7 mg/d, CaD- 1,039+/- 635.1 mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Jackson et al., 2011	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity, Height; Other - Whole-Body Bone Area, Percent Lean Mass, Physical Activity, Baseline Hormone Use And Hormone Therapy Trial Randomization (Final Model Nr)	Secondary-Intertrochanteric BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	0.746 (sd=0.136)	final=0.749 (sd=0.135)	+0.02 (0.01, 0.04)	.
					D3 placebo		751	0.725 (sd=0.134)	final=0.725 (sd=0.137)		.
				Secondary-Narrow Neck BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	0.736 (sd=0.129)	final=0.742 (sd=0.133)	+0.02 (0.01, 0.03)	0.003
					D3 placebo		751	0.723 (sd=0.131)	final=0.722 (sd=0.136)		.
				Secondary-Shaft BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	1.18 (sd=0.181)	final=1.199 (sd=0.189)	+0.03 (0.01, 0.05)	.
					D3 placebo		751	1.155 (sd=0.181)	final=1.165 (sd=0.190)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Jackson et al., 2011	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jacobs et al., 2011	Nested Case Control	breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 y.		Women's Healthy Eating and Living (WHEL)	Government	USA; multiple	1024/500/100	51.9 (9.0)/NR	Non-Hispanic White=857; Hispanic=53; Non-Hispanic Black=29	Cancer in remission	All: deficient (<10ng/ml) 51, insufficient (>=10, <20) 282, suboptimal (>=20, <30) 410, optimal (>=30) 281

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jacobs et al., 2011	Nested Case Control	clinical site, cancer stage, age at cancer diagnosis, date of random assignment into the WHEL Study, and date of original cancer diagnosis	NR	Primary-Mortality	25(OH)D	Insufficient, <20 ng/ml	7.3 yrs	nr/164	adjusted/OR	1.13	0.72, 1.79	0.59
				Primary-Breast Cancer	25(OH)D	Sufficient, =20 ng/ml	7.3 yrs	nr/336	adjusted/OR	1	Reference	
					25(OH)D	<10ng/mL(deficient)	NR	nr/51	adjusted/OR	1.14	0.57, 2.31	
					25(OH)D	>=10 and <20ng/mL(insufficient)	NR	nr/282	adjusted/OR	1	0.68, 1.48	
					25(OH)D	>=20 and <30ng/mL(suboptimal)	NR	nr/410	adjusted/OR	1.05	0.76, 1.47	
					25(OH)D	>=30ng/mL(optimal)	NR	nr/281	adjusted/OR	1	reference	0.850
					25(OH)D	<10ng/mL(deficient)- Premenopausal women	NR	nr/6	adjusted/OR	0.17	0.01, 4.56	
					25(OH)D	>=10 and <20ng/mL(insufficient)- Premenopausal women	NR	nr/31	adjusted/OR	1.02	0.33, 3.16	
					25(OH)D	>=20 and <30ng/mL(suboptimal)- Premenopausal women	NR	nr/45	adjusted/OR	1.76	0.64, 4.87	
					25(OH)D	>=30ng/mL(optimal)- Premenopausal women	NR	nr/36	adjusted/OR	1	reference	0.610
					25(OH)D	<10ng/mL- Postmenopausal women	NR	nr/37	adjusted/OR	1.45	0.62,3.37	
					25(OH)D	>=10 and <20ng/mL- Postmenopausal women	NR	nr/202	adjusted/OR	1.09	0.68, 1.76	
					25(OH)D	>=20 and <30ng/mL- Postmenopausal women	NR	nr/266	adjusted/OR	0.9	0.60, 1.36	
					25(OH)D	>=30ng/mL- Postmenopausal women	NR	nr/187	adjusted/OR	1	reference	0.490
				Primary-Lethal Breast Cancer	25(OH)D	<20ng/mL(insufficient)	NR	nr/164	adjusted/OR	1.13	0.72, 1.79	
					25(OH)D	>=20ng/mL(sufficient)	NR	nr/336	adjusted/OR	1	reference	0.590

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jacobs et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jacobse n et al., 2012	Prospective Cohort	51–70 years; without prior history of ischemic heart disease	Not specified	Copenhagen City Heart Study	university and hospital fund	Copenhagen, Denmark	10170/10170/56	57 (49–66)/NR		Not Reported	25(OH)D level-44nmol/L(26–58)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jacobson et al., 2012	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Sex, Age; Anthropometrics- BMI; Medical Conditions- Diabetes, Plasma Total Cholesterol, High-Density Lipoprotein Cholesterol, Systolic Blood Pressure, And Estimated Glomerular Filtration Rate; Sun Exposure- Month Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption	Primary-Nonfatal Ischemic Heart Disease	25(OH)D	<25.0 nmol/L	29 yrs	381/2553	Adjusted/HR	1.08	0.85, 1.37	0.1
					25(OH)D	25.0–49.9 nmol/L	29 yrs	648/4068	Adjusted/HR	1.01	0.81, 1.26	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	391/2470	Adjusted/HR	0.91	0.72, 1.15	
				Primary-Nonfatal MI	25(OH)D	≥75.0 nmol/L	29 yrs	158/1079	Adjusted/HR	1	Reference	
					25(OH)D	<25.0 nmol/L	29 yrs	224/2553	Adjusted/HR	1.17	0.83, 1.63	0.4
					25(OH)D	25.0–49.9 nmol/L	29 yrs	350/4068	Adjusted/HR	0.97	0.71, 1.34	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	228/2470	Adjusted/HR	1.02	0.74, 1.42	
					25(OH)D	≥75.0 nmol/L	29 yrs	89/1079	Adjusted/HR	1	Reference	
				Primary-Fatal Ischemic Heart Disease/MI	25(OH)D	<25.0 nmol/L	29 yrs	422/2553	Adjusted/HR	1.53	1.18, 1.98	<0.001
					25(OH)D	25.0–49.9 nmol/L	29 yrs	627/4068	Adjusted/HR	1.23	0.96, 1.58	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	367/2470	Adjusted/HR	1.18	0.91, 1.54	
					25(OH)D	≥75.0 nmol/L	29 yrs	106/1079	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jacobson et al., 2012	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jacobse n et al., 2013	Prospective Cohort	51–70 years; had 25(OH)D measurement	Not specified	Copenhagen City Heart Study	University and hospital fund	Copenhagen, Denmark	10170/10170/56	56 (48–65)/NR			25(OH)D level-44nmol/L(26–58)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jacobse n et al., 2013	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Medical Conditions- Hypertension, Diabetes Mellitus, Atrial Fibrillation, Use Of Antihypertensive Medication, Plasma Total Cholesterol, HDL Cholesterol, Estimated Glomerular Filtration; Sun Exposure- Month Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption	Primary-Ischemic Stroke	25(OH)D	<25.0 nmol/L	29 yrs	350/2553	Adjusted/HR	1.36	1.09, 1.70	<0.001
					25(OH)D	25.0–49.9 nmol/L	29 yrs	504/4068	Adjusted/HR	1.1	0.89, 1.36	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	277/2470	Adjusted/HR	0.92	0.74, 1.16	
					25(OH)D	>=75.0 nmol/L	29 yrs	125/1079	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jacobson et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	NA	Y	Y	N	A	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jassal et al., 2010	Prospective Cohort	Caucasian; middle-class; community dwelling adults; Not specified	lacked 25(OH)D, 1, 25(OH)2D and PTH measurements; eGFR < 15mL/min/1.73 m ²	Rancho Bernardo Study	Government	USA; San Diego, CA	1073/1073/62 %	74 (10)/NR	Non-Hispanic White=100	Not Reported	25(OH)D - 42(14) ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jassal et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI, Medical Conditions - Prevalent Cardiovascular Disease; Medical Conditions- Prevalent Cvd; Smoking, Other Lifestyle Factors- Exercise, Sun Exposure, Season Of Blood Draw; Other - Systolic Blood Pressure, LDL Cholesterol, Fasting Glucose, Log (Urine Albumin/Creatinine Ratio), eGFR	Primary- Cardiovascular Mortality	25(OH)D	per SD increase in serum 25(OH)D	10.4 yrs	111/1073	Adjusted/HR	1.07	0.86, 1.33	NS
					1,25(OH)2D	per SD increase in log of serum 1,25(OH)2D	10.4 yrs	111/1073	Adjusted/HR	0.98	0.80, 1.21	NS

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jassal et al., 2010	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	should get ref 21 to verify eligibility criteria and sampling method --- Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jenab et al., 2010	Nested Case Control	19–50 years; 51–70 years; geographic or administrative boundaries at each study center; age 25–82 (mostly 35–70)	anal cancer; missing matching information; missing laboratory 25-(OH) D data	EPIC	Government	Germany (specify city, if given);UK;Denmark, France, Greece, Italy, the Netherlands, Norway, Spain, Sweden	2496/2496/50.3	58.6 (7.2)/30.3–76.6		Not Reported	Circulating 25-(OH)D geometric mean (5th–95th percentile): colon cases- 51.7 nmol/L (24.1–104.4) controls- 57.2 nmol/L (28.0–114.8) rectal cases- 54.9 nmol/L (26.3–111.0) controls- 55.4 nmol/L (24.7–116.5)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jenab et al., 2010	Nested Case Control	age (plus or minus six months at recruitment), sex, study center, time of the day at blood collection, and fasting status at the time of blood collection (less than three hours, three to six hours, and more than six hours). Women were further matched by m	Other Nutrients Or Dietary Factors- Total Dietary Energy Consumption, Intake Of Total Fruits, Vegetables, Meat Or Meat Products; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- Body Mass Index; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Smoking Status/Duration/Intensity, Total Physical Activity, Alcohol; Other - Time Of The Day At Blood Collection, Fasting Status At The Time Of Blood Collection, Menopausal Status, Phase Of Menstrual Cycle At Time Of Blood Collection, Usage Of Hormone Replacement Therapy At Time Of Blood Collection	Primary-Colorectal Cancer	25(OH)D	Quintile 1: <25nmol/l	NR	64/116	adjusted/HR	1.32	0.87, 2.01	NR
					25(OH)D	Quintile 2: >=25<50nmol/l	NR	473/873	adjusted/HR	1.28	1.05, 1.56	NR
					25(OH)D	Quintile 3: >=50<75nmol/l	NR	448/909	adjusted/HR	1	reference	NR
					25(OH)D	Quintile 4: >=75<100nmol/l	NR	173/382	adjusted/HR	0.88	0.68, 1.13	<0.001
				Primary-Colon Cancer	25(OH)D	Quintile 5: >=100nmol/l	NR	90/216	adjusted/HR	0.77	0.56, 1.06	<0.001
					25(OH)D	Quintile 1: <25nmol/l	NR	45/72	adjusted/HR	1.9	1.10, 3.29	NR
					25(OH)D	Quintile 2: >=25<50nmol/l	NR	300/549	adjusted/HR	1.36	1.05, 1.76	NR
					25(OH)D	Quintile 3: >=50<75nmol/l	NR	286/581	adjusted/HR	1	reference	NR
					25(OH)D	Quintile 4: >=75<100nmol/l	NR	104/242	adjusted/HR	0.86	0.62, 1.17	<0.001
				Primary-Rectum Cancer	25(OH)D	Quintile 5: >=100nmol/l	NR	50/126	adjusted/HR	0.71	0.46, 1.08	<0.001
					25(OH)D	Quintile 1: <25nmol/l	NR	NR/NR	adjusted/HR	0.77	0.37, 1.59	NR
					25(OH)D	Quintile 2: >=25<50nmol/l	NR	NR/NR	adjusted/HR	1.17	0.84, 1.65	NR
					25(OH)D	Quintile 3: >=50<75nmol/l	NR	NR/NR	adjusted/HR	1	reference	NR
					25(OH)D	Quintile 4: >=75<100nmol/l	NR	NR/NR	adjusted/HR	0.93	0.60, 1.45	0.288
					25(OH)D	Quintile 5: >=100nmol/l	NR	NR/NR	adjusted/HR	0.82	0.48, 1.40	0.320

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jenab et al., 2010	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	B	cases ascertained from cancer registries, not verified independently Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Johansson et al., 2012	Prospective Cohort	70–81 years; able to walk without aids; give signed informed consent; provide self-reported data	Not specified	MrOS	Unclear	Sweden: Gothenberg, Malmö, Uppsala	2878/2878/0	75.7/3.4		Other; some with diabetes, htn, cancer, stroke, MI, angina	<25 nmol/l - 20 (74); 25–49 nmol/l 373 (75); 50–74 nmol/l- 735(57); 75–99 nmol/l- 317(42); ≥100 nmol/l- 106(34)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Johansson et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Current Age; Medical Conditions- Past History Of Cancer, Angina, Diabetes; Smoking, Other Lifestyle Factors- Outdoor Activity, Physical Activity Walking; Other - Current Time Since Baseline, Total Hip BMD, General Health	Primary-Death	25(OH)D	per SD decrease	8.2 yrs	577/2878	adjusted/HR	1.16	1.06, 1.26	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Johansson et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Johnson et al., 2012	RCT/CCT	Postmenopausal women; Postmenopausal women; 50–79 years of age	previous history of breast cancer, history of other cancers within the previous 10 years, medical conditions likely to result in death within 3 years, conditions likely to interfere with retention in the study	WHI Mammogram Density Ancillary Study	Government	USA	492/330/100	62 (8)/NR	Non-Hispanic White=48; Hispanic=12; Non-Hispanic Black=36; Asian=4	Post menopausal	Table 1 (need to discuss what to enter)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Johnson et al., 2012	RCT/CCT	NR	NR	Secondary-Percent Mammographic Density	D3 (Vit D3 400 IU+1,000 mg calcium)/day-overall		179	3.7 (2.9, 4.8)	final=3.6 (2.9, 4.6)	+0.8 (-0.2, 1.8)	0.1
					D3 placebo-overall		151	2.8 (2.1, 3.7)	final=2.8 (2.2, 3.7)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline < 200 IU/day		87	3.6 (2.5, 5.2)	final=3.5 (2.5, 4.9)	+0.5 (-0.9, 1.9)	0.47
					D3 placebo-Vit D intake at baseline < 200 IU/day		77	3 (2.1, 4.5)	final=3 (2.1, 4.3)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline >= 400 IU/day		53	4.3 (2.9, 6.4)	final=4 (2.6, 6.0)	+1.7 (-0.1, 3.5)	0.07
					D3 placebo-Vit D intake at baseline >= 400 IU/day		44	2.7 (1.5, 4.8)	final=2.3 (1.3, 4.2)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline 200 ~ 400 IU/day		29	2.4 (1.1, 5.3)	final=2.8 (1.4, 5.6)	-0.4 (-2.5, 1.7)	.
					D3 placebo-Vit D intake at baseline 200 ~ 400 IU/day		24	2.5 (1.3, 5.1)	final=3.2 (1.7, 6.1)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Johnson et al., 2012	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jones et al., 2012	Prospective Cohort	Pregnant or lactating women; Healthy; nonsmoking; healthy, uncomplicated term pregnancy; >=2 frozen CB serum samples in storage; allergic outcomes assessed at 12 months of age (offspring)	Not specified		Government	Australia;Perth	231/231/48.5 (neonatal)	33.4 (4.5)/NR	Non-Hispanic White=797; Asian=39; Race_other1=26		The mean (SD) CB 25(OH)D3 = 58.4 (24.1) nmol/L, range= 9.18 to 246.34 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jones et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Infant Gender, Maternal Age, Maternal Ethnicity; Sun Exposure-Season Of Birth	Primary-Eczema	25(OH)D3	per 10 nmol/L rise in CB 25(OH)D3	NR	78/231	adjusted/OR	0.857	0.739, 0.995	0.042

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jones et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	Y	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jorde et al., 2010	RCT/CCT	19–50 years; 51–70 years; 21–70 years; BMI between 28.0–47.0 kg/m ² ; without a history of diabetes, coronary infarction, angina pectoris, stroke, renal stone disease, or sarcoidosis	Pregnant; lactating; women <50 years of age without adequate contraception; serum calcium>2.55 mmol/ L; males with serum creatinine >129 umol/ L; females with serum creatinine >104 umol/L		Manufacturer	Norway	438/330/64.2	47.5 (11.4)/NR		Overweight/obese; Other; using blood pressure or lipid lowering medication	58.0 ± 21.1 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Jorde et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender	Secondary-DBP	D3 DD (40,000 IU Vit D3/week)+500 mg calcium/day		114	76.5 (sd=9.8)	change=1.0 (sd=7.4)	+0.8 (-1.3, 2.9)	.
					D3 DP (20,000 IU Vit D3/week)+500 mg calcium/day		104	74.9 (sd=9.5)	change=1.0 (sd=8.3)	+0.8 (-1.4, 3.0)	.
					D3 PP (placebo)+500 mg calcium/day		112	74.8 (sd=10.0)	change=0.2 (sd=8.3)		.
				Secondary-SBP	D3 DD (40,000 IU Vit D3/week)+500 mg calcium/day		114	124 (sd=15)	change=1.2 (sd=11.4)	+2.3 (-0.9, 5.5)	.
					D3 DP (20,000 IU Vit D3/week)+500 mg calcium/day		104	121 (sd=13)	change=3.5 (sd=11.8)	+4.6 (1.3, 7.9)	.
					D3 PP (placebo)+500 mg calcium/day		112	125 (sd=16)	change=-1.1 (sd=12.8)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Jorde et al., 2010	RCT/CCT	ND	ND	ND	N	Y	Y	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jorde et al., 2010	RCT/CCT	19–50 years; 51–70 years; 21–70 years; BMI 28.0–47.0 kg/m ²	bisphosphonates; estrogen; h/o coronary infarction, angina; diabetes; stroke; renal stone disease; sarcoidosis; serum calcium > 2.55 mmol/L; males with serum creatinine > 129 µmol/L and females with serum creatinine > 104 µmol/L; using estrogen		Manufacturer	Norway	421/312/NR	50.8 (10.7)/NR		Overweight/obese	57.7 +/-20.7 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Jorde et al., 2010	RCT/CCT	NR	NR	Secondary-BMD L2-L4	D3 DD (Vit D3 40,000 IU/week+500 mg calcium)		110	1.27 (sd=0.155)	change=0.008 (sd=0.036)	+0.00 (-0.01, 0.01)	.
					D3 DP (Vit D3 20,000 IU/week+500 mg calcium)		97	1.235 (sd=0.161)	change=0.008 (sd=0.039)	+0.01 (0.0, 0.01)	.
					D3 PP (Placebo+500 mg calcium)		105	1.251 (sd=0.170)	change=0.007 (sd=0.042)		.
				Secondary-BMD Total Hip	D3 DD (Vit D3 40,000 IU/week+500 mg calcium)		110	1.107 (sd=0.133)	change=0.008 (sd=0.014)	-0.00 (-0.01, 0.0)	.
					D3 DP (Vit D3 20,000 IU/week+500 mg calcium)		97	1.067 (sd=0.128)	change=0.011 (sd=0.014)	+0.0 (-0.0, 0.01)	.
					D3 PP (Placebo+500 mg calcium)		105	1.092 (sd=0.130)	change=0.009 (sd=0.017)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Jorde et al., 2010	RCT/CCT	ND	ND	ND	N	Y	Y	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kalra et al., 2012	RCT/CCT	Pregnant or lactating women; between 12–24 weeks gestation	Not specified		Government	Lucknow, India	299/71/100	26.7 (4.0)/NR			Group 1–31.7 nmol/L (IQR 14.0–57.2) Group 2- 32.0 nmol/L (IQR 14.5–45.7)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Kalra et al., 2012	RCT/CCT	NR	NR	Secondary-Birth Weight	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		35	NR (NR)	Final=3.03 (1.71, 4.35)	-0.05 (-1.92, 1.82)	0.96
					1500 mg cholecalciferol (one dose 2nd trimester)		36	NR (NR)	Final=3.08 (1.71, 4.45)	.	
				Secondary-Weight At 3 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		33	NR (NR)	Final=5.9 (5.8, 6.0)	+0 (-0.1, 0.1)	1
					1500 mg cholecalciferol (one dose 2nd trimester)		31	NR (NR)	Final=5.9 (5.8, 6.0)	.	
				Secondary-Weight At 6 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		24	NR (NR)	Final=7.3 (7.1, 7.5)	+0.1 (-0.1, 0.3)	0.37
					1500 mg cholecalciferol (one dose 2nd trimester)		28	NR (NR)	Final=7.2 (7.0, 7.4)	.	
				Secondary-Weight At 9 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		18	NR (NR)	Final=8.5 (8.3, 8.7)	+0.1 (-0.3, 0.5)	0.58
					1500 mg cholecalciferol (one dose 2nd trimester)		22	NR (NR)	Final=8.4 (8.1, 8.7)	.	
				Secondary-Length At Birth	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		35	NR (NR)	Final=50.1 (49.8, 50.4)	-0.2 (-0.6, 0.2)	0.35
					1500 mg cholecalciferol (one dose 2nd trimester)		36	NR (NR)	Final=50.3 (50.0, 50.6)	.	
				Secondary-Length At 3 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		33	NR (NR)	Final=59.9 (59.5, 60.3)	+0.1 (-0.6, 0.8)	0.79
					1500 mg cholecalciferol (one dose 2nd trimester)		31	NR (NR)	Final=59.8 (59.2, 60.4)	.	

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-Length At 6 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		24	NR (NR)	Final=64.9 (64.0, 65.8)	+0.6 (-0.5, 1.7)	0.28
					1500 mg cholecalciferol (one dose 2nd trimester)		28	NR (NR)	Final=64.3 (63.6, 65.0)	.	
				Secondary-Length At 9 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		18	NR (NR)	Final=69.9 (69.2, 70.6)	+0.6 (-0.5, 1.7)	0.27
					1500 mg cholecalciferol (one dose 2nd trimester)		22	NR (NR)	Final=69.3 (68.5, 70.1)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Kalra et al., 2012	RCT/CCT	Y	ND	Y	N	ND	ND	ND	ND	Y	C	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Karakas et al., 2013	Prospective Cohort	Healthy; middle-aged	missing values; self-reported prevalent CHD; missing blood samples	MONICA/KO RA Augsburg case-cohort study	Government	Germany (specify city, if given)	1783/964/24.5	51.9 (0.42)/35–74			male cases- 37.7(1.03), non-cases 43.9(1.02)\ female cases- 31.9(1.05), non-cases 39.7(1.01)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Karakas et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Sun Exposure- Season Of Blood Sampling; Other - Traditional Cardiovascular Risk Factors, CRP, IL-6, Sicam-1, Ip-10	Primary-Coronary Heart Disease	25(OH)D in men	54.14–153.92 nmol/L	11 yrs	225/964	Adjusted/HR	0.84	0.52, 1.35	0.461
					25(OH)D in men	35.05–54.13 nmol/L	11 yrs		Adjusted/HR	0.66	0.43, 1.02	
					25(OH)D in men	5.08–35.02 nmol/L	11 yrs		Adjusted/HR	1	Reference	
					25(OH)D in women	47.70–127.69 nmol/L	11 yrs	73/819	Adjusted/HR	0.42	0.19, 0.93	0.028
					25(OH)D in women	33.16–47.69 nmol/L	11 yrs		Adjusted/HR	0.67	0.35, 1.29	
					25(OH)D in women	9.87–33.15 nmol/L	11 yrs		Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Karakas et al., 2013	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Karkkainen et al., 2010	RCT/CCT	age at a minimum of 65 years at the end of November 2002;; living in the Kuopio Province at the onset of the trial;; not belonging to the former OSTPRE bone densitometry sample.	Not specified	OSTPRE-FPS	Manufacturer	Finland; Kuopio	750/591/100	67.4 (1.9)/NR		Post menopausal	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Karkkainen et al., 2010	RCT/CCT	NR	NR	Secondary-Femoral Neck BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.866 (sd=0.13)	final=0.848 (sd=0.13)	-0.002 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		311	0.865 (sd=0.12)	final=0.850 (sd=0.12)		.
				Secondary-Lumbar Spine BMD	D3 Vit D 800 IU+calcium 1,000 mg		259	1.039 (sd=0.17)	final=1.047 (sd=0.17)	-0.013 (-0.041, 0.016)	.
					D3 control (neither supplementation nor placebo)		285	1.052 (sd=0.17)	final=1.060 (sd=0.17)		.
				Secondary-Total Body BMD	D3 Vit D 800 IU+calcium 1,000 mg		195	1.069 (sd=0.09)	final=1.078 (sd=0.10)	-0.003 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		238	1.079 (sd=0.09)	final=1.081 (sd=0.10)		.
				Secondary-Total Proximal Femur BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.948 (sd=0.14)	final=0.934 (sd=0.14)	-0.005 (-0.03, 0.02)	.
					D3 control (neither supplementation nor placebo)		310	0.953 (sd=0.13)	final=0.939 (sd=0.13)		.
				Secondary-Trochanter BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.783 (sd=0.14)	final=0.779 (sd=0.13)	-0.01 (-0.03, 0.01)	.
					D3 control (neither supplementation nor placebo)		310	0.797 (sd=0.13)	final=0.790 (sd=0.13)		.
				Secondary-Ward's Triangle	D3 Vit D 800 IU+calcium 1,000 mg		280	0.67 (sd=0.15)	final=0.652 (sd=0.14)	-0.001 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		310	0.672 (sd=0.13)	final=0.653 (sd=0.13)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Karkkainen et al., 2010	RCT/CCT	ND	ND	N	Y	N	Y	N	N	N	C	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Karkkainen et al., 2010	RCT/CCT	age at a minimum of 65 years at the end of November 2002.; living in Kuopio province area at the onset of the trial; not belonging to the former OSTPRE bone densitometry sample.; ambulatory women		OSTRE-FPS	Private	Finland; Kuopio	3139/3139/100	67.4 (1.9)/65–71			Mean 25(OH)D concentrations (nmol/L): intervention- 50.1 (18.8) ;control- 49.2 (17.7) (P = 0.544)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Karkkainen et al., 2010	RCT/CCT	NR	NR	Primary-No Falls	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	754/1566	Crude/OR	1.05	0.91, 1.20	>0.05
					Placebo; Ca	Placebo	3 y	740/1573	Crude/OR	1	Reference	
				Primary-Falls (>=1)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1109/1566	Crude/OR	1.13	0.97, 1.32	>0.05
					Placebo; Ca	Placebo	3 y	1073/1573	Crude/OR	1	Reference	
				Primary-No Fall Requiring Medical Attention (FRMA)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1308/1566	Crude/OR	0.84	0.70, 1.01	>0.05
					Placebo; Ca	Placebo	3 y	1274/1573	Crude/OR	1	Reference	
				Primary-Falls Requiring Medical Attention (FRMA) (=1)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1488/1566	Crude/OR	0.72	0.53, 0.97	0.03
					Placebo; Ca	Placebo	3 y	1466/1573	Crude/OR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Karkkainen et al., 2010	RCT/CCT	ND	ND	N	Y	N	Y	N	N	Y	C	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Kestenbaum et al., 2011	Prospective Cohort	51–70 years; >65 years; ambulatory	use of a wheelchair in the home; current treatment for cancer; institutionalization;; need for a proxy respondent to provide informed consent; plans to move from the area within 3 years	CHS	Government	USA; Forsyth County, NC, Sacramento county, CA, Washington County, MD, Pittsburgh, PA	2312/2312/58	73 (4)/NR	Non-Hispanic Black=4		25.2+/- _ 10.2 ng/ml (interquartile range: 17.8 to 31.5 ng/ml).	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kestenbaum et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race, Education; Anthropometrics- BMI; Medical Conditions- Diabetes, Hypertension; Sun Exposure- Season Of The Year; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Systolic Blood Pressure, Levels Of C-Reactive Protein, HDL Cholesterol, Calcium And Phosphorus, eGFR	Primary-All-Cause Mortality	25(OH)D	>30 ng/ml	14 yrs	329/681	adjusted/HR	1	reference	
					25(OH)D	15–30 ng/ml	14 yrs	668/1247	adjusted/HR	1.15	1.00, 1.33	
					25(OH)D	<15 ng/ml	14 yrs	229/384	adjusted/HR	1.29	1.05, 1.57	
				Primary-Cardiovascular Mortality	25(OH)D	continuous per 10 ng/ml	14 yrs	1226/2312	adjusted/HR	1.09	1.02, 1.17	0.012
					25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	389/2312	Adjusted/HR	1.06	0.94, 1.19	0.356
					25(OH)D	<15ng/ml	14 yrs	107/681	Adjusted/HR	1.17	0.83, 1.67	
					25(OH)D	15–30 ng/ml	14 yrs	207/1247	Adjusted/HR	1.01	0.78, 1.30	
					25(OH)D	>30 ng/ml	14 yrs	75/384	Adjusted/HR	1	Reference	
				Primary-Incident Heart Failure	25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	504/2312	Adjusted/HR	0.95	0.86, 1.05	0.303
					25(OH)D	<15ng/ml	14 yrs	107/681	Adjusted/HR	1.17	0.83, 1.67	
					25(OH)D	15–30 ng/ml	14 yrs	207/1247	Adjusted/HR	1.01	0.78, 1.30	
					25(OH)D	>30 ng/ml	14 yrs	75/384	Adjusted/HR	1	Reference	
				Primary-Incident Myocardial Infarction	25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	299/2312	Adjusted/HR	1.25	1.08, 1.44	0.002
					25(OH)D	<15ng/ml	14 yrs	88/681	Adjusted/HR	1.4	0.93, 2.12	
					25(OH)D	15–30 ng/ml	14 yrs	161/1247	Adjusted/HR	1.2	0.90, 1.59	
					25(OH)D	>30 ng/ml	14 yrs	50/384	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kestenbaum et al., 2011	Y	Y	N	N						

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Khadiolkar et al., 2010	RCT/CCT	9–18 years; postmenarcheal; 14–15 years; attending a state run school from Feb 2006-April 2007	Not specified		Unclear	Pune, India	50/49/100	14.6/14.3–15.3		Not Reported	Vit D + Ca- 24.5 nmol/L (12.7–33.2) Placebo +Ca- 20.8 nmol/L (12.7–30.4)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Khadilkar et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Height, Weight; Other - Calcium Compliance, Baseline Value Of Dietary Calcium Intake	Secondary-L2-L4 Bone Mineral Apparent Density	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=4.2 (0.6, 9.3)	+0.5 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=3.7 (1.0, 7.7)		.
				Secondary-L2-L4 BMC	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=10.5 (4.6, 17.2)	-0.8 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=11.3 (5.4, 18.0)		.
				Secondary-Total BMC	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=10.1 (6.1, 14.7)	+1.9 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=8.2 (4.9, 12.6)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Khadilkar et al., 2010	RCT/CCT	ND	ND	ND	Y	Y	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kilkinen et al., 2009	Prospective Cohort	30 years or more	Current cardiovascular disease; lacking serum sample for 25(OH)D analysis	Mini-Finland Health Survey	Government	Finland;40 areas	6219/6219/54.7	49.4 (13.6)/NR			43.4 +/-19.7 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kilkinen et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Marital Status, Education; Anthropometrics- BMI; Medical Conditions- Diabetes, Blood Pressure; Smoking, Other Lifestyle Factors- Smoking, Physical Activity, Alcohol Consumption, HDL and LDL Cholesterol	Primary- Cardiovascular Death	25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	27.1 yrs (median)	150/1253	Adjusted/HR	0.76	0.61, 0.95	0.005
					25(OH)D	M:48.0–61.0 nmol/l F:44.0–55.0 nmol/l	27.1 yrs (median)	171/1222	Adjusted/HR	0.86	0.70, 1.06	
					25(OH)D	M:38.0–47.0 nmol/l F:34.0–43.0 nmol/l	27.1 yrs (median)	164/1284	Adjusted/HR	0.81	0.66, 1.00	
					25(OH)D	M:29.0–37.0 nmol/l F:26.0–33.0 nmol/l	27.1 yrs (median)	194/1202	Adjusted/HR	1.04	0.86, 1.26	
				Primary- Cerebrovascular Death	25(OH)D	M:5.0–28.0 nmol/l F:4.0–25.0 nmol/l	27.1 yrs (median)	254/1258	Adjusted/HR	1	Reference	
					25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	27.1 yrs (median)	33/1253	Adjusted/HR	0.48	0.31, 0.75	0.002
					25(OH)D	M:48.0–61.0 nmol/l F:44.0–55.0 nmol/l	27.1 yrs (median)	48/1222	Adjusted/HR	0.69	0.48, 1.00	
					25(OH)D	M:38.0–47.0 nmol/l F:34.0–43.0 nmol/l	27.1 yrs (median)	68/1284	Adjusted/HR	0.97	0.70, 1.35	
					25(OH)D	M:29.0–37.0 nmol/l F:26.0–33.0 nmol/l	27.1 yrs (median)	52/1202	Adjusted/HR	0.8	0.57, 1.14	
					25(OH)D	M:5.0–28.0 nmol/l F:4.0–25.0 nmol/l	27.1 yrs (median)	92/1258	Adjusted/HR	1	Reference	
				Primary-Coronary Disease Death	25(OH)D	M:62–180 nmol/l F:56.0–151.0 nmol/l	27.1 yrs (median)	117/1253	Adjusted/HR	0.91	0.70, 1.18	0.2
					25(OH)D	M:48.0–61.0 nmol/l F:44.0–55.0 nmol/l	27.1 yrs (median)	123/1222	Adjusted/HR	0.95	0.74, 1.22	
					25(OH)D	M:38.0–47.0 nmol/l F:34.0–43.0 nmol/l	27.1 yrs (median)	96/1284	Adjusted/HR	0.73	0.56, 0.95	
					25(OH)D	M:29.0–37.0 nmol/l F:26.0–33.0 nmol/l	27.1 yrs (median)	142/1202	Adjusted/HR	1.17	0.93, 1.48	
					25(OH)D	M:5.0–28.0 nmol/l F:4.0–25.0 nmol/l	27.1 yrs (median)	162/1258	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kilkinen et al., 2009	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kritchevsky et al., 2012	Prospective Cohort	70–79; community dwelling; black and white; no difficulty walking 0.25 miles, climbing 10 steps and performing basic ADLs; not enrolled in lifestyle intervention trials	PTH >250 pg/ml; 25(OH)D >75.25 pg/ml	Health ABC	Government	USA; Pittsburgh, Memphis	3075/2638/51.2	74.7 (2.9)/NR	Non-Hispanic White=61; Non-Hispanic Black=39	Other; well-functioning	serum 25(OH)D: 25.8 (10.3) ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kritchevs ky et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender, Race, Education; Anthropometrics- BMI; Medical Conditions- Prevalent Diabetes, Hypertension, CVD, Cancer, Lung Disease; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status, Pack-Years, Alcohol Consumption, Time Walking, Usual 20-M Walking Speed; Other - Cognition, Depressive Symptoms, Cholesterol, PTH	Primary-All-Cause Mortality	25(OH)D	< 10 ng/ml	8.5 yrs	44/108	adjusted/HR	2.27	1.59, 3.24	<0.001
					25(OH)D	10 to <20 ng/ml	8.5 yrs	241/750	adjusted/HR	1.48	1.20, 1.84	
					25(OH)D	20 to <30 ng/ml	8.5 yrs	229/931	adjusted/HR	1.25	1.02, 1.52	
					25(OH)D	>=30 ng/ml	8.5 yrs	177/849	adjusted/HR	1	Reference	
					25(OH)D	< 10 ng/ml-whites	8.5 yrs	10/25	adjusted/HR	2.02	1.02, 3.99	0.001
					25(OH)D	10 to <20 ng/ml-whites	8.5 yrs	82/279	adjusted/HR	1.54	1.16, 2.06	
					25(OH)D	20 to <30 ng/ml-whites	8.5 yrs	138/620	adjusted/HR	1.22	0.96, 1.55	
					25(OH)D	>=30 ng/ml-whites	8.5 yrs	143/691	adjusted/HR	1	Reference	
					25(OH)D	< 10 ng/ml-blacks	8.5 yrs	34/83	adjusted/HR	2.59	1.57, 4.26	<0.001
					25(OH)D	10 to <20 ng/ml-blacks	8.5 yrs	159/471	adjusted/HR	1.76	1.20, 2.57	
					25(OH)D	20 to <30 ng/ml-blacks	8.5 yrs	91/311	adjusted/HR	1.6	1.07, 2.39	
					25(OH)D	>=30 ng/ml-blacks	8.5 yrs	34/158	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kritchevs ky et al., 2012	Y	Y	N	N						

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kuhn et al., 2013	Prospective Cohort	Not specified	MI or stroke; without complete follow-up information; missing 25(OH)D values; missing covariate data	EPIC-Germany	Government	Germany (specify city, if given);Heidelberg, Potsdam	3115/2132/NR	NR (NR)/NR		Not Reported	plasma 25(OH)D of the 2132 sub cohort- 47.2 +/- 18.3 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kuhn et al., 2013	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI, Waist Circumference; Sun Exposure- Center; Smoking, Other Lifestyle Factors- Alcohol Intake, Smoking, Physical Activity	Primary-Myocardial Infarction	25(OH)D	Q4: median 66.5	7.6 yrs	118/533	adjusted/HR	1	Reference	0.19
					25(OH)D	Q3: median 50.5	7.6 yrs	117/533	adjusted/HR	0.95	0.70, 1.28	
					25(OH)D	Q2: median 40.4	7.6 yrs	158/533	adjusted/HR	1.24	0.93, 1.66	
					25(OH)D	Q1: median 28.9	7.6 yrs	166/533	adjusted/HR	1.43	1.07, 1.92	
				Primary-Stroke	25(OH)D	Q4: median 66.6	7.6 yrs	111/533	adjusted/HR	1	Reference	0.19
					25(OH)D	Q3: median 50.5	7.6 yrs	101/533	adjusted/HR	0.86	0.63, 1.17	
					25(OH)D	Q2: median 40.4	7.6 yrs	102/533	adjusted/HR	0.83	0.61, 1.12	
					25(OH)D	Q1: median 28.9	7.6 yrs	157/533	adjusted/HR	1.37	1.02, 1.84	
				Primary-Cvd As Composite Endpoint	25(OH)D	Q4: median 66.5	7.6 yrs	229/533	adjusted/HR	1	Reference	0.12
					25(OH)D	Q3: median 50.5	7.6 yrs	218/533	adjusted/HR	0.89	0.70, 1.14	
					25(OH)D	Q2: median 40.4	7.6 yrs	260/533	adjusted/HR	1.06	0.83, 1.35	
					25(OH)D	Q1: median 28.9	7.6 yrs	323/533	adjusted/HR	1.41	1.11, 1.79	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kuhn et al., 2013	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	ref 25 might be helpful reconciled

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kuhn et al., 2013	Nested Case Control	Varied by country: generally adults 40–65	Not specified	EPIC	Private Foundation	Multiple Countries	2,782/2782/100	50.7 (8.8)/NR			reported in quartiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kuhn et al., 2013	Nested Case Control	study center, age±3 months, menopausal status, exogenous hormone use at blood donation, time of day of blood collection, fasting status, phase of cycle	Demographics (Age, Sex, Race/Ethnicity)- Educational Level; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Alcohol Consumption, Smoking, Physical Activity; Other - Number Of Full-Term Pregnancies, Breastfeeding	Primary-Breast Cancer	25(OH)D	Q1: <=39.3	4.1 yrs	342/688	adjusted/OR	1	reference	0.67
					25(OH)D	Q2: 39.4–50.9	4.1 yrs	357/707	adjusted/OR	1.03	0.83, 1.29	
					25(OH)D	Q3: 51.0–63.0	4.1 yrs	324/670	adjusted/OR	0.94	0.74, 1.19	
					25(OH)D	Q4: >63.0	4.1 yrs	368/717	adjusted/OR	1.07	0.85, 1.36	
					25(OH)D	log2 (continuous)	4.1 yrs	1391/2782	adjusted/OR	1.01	0.86, 1.19	0.86

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kuhn et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	Y	N	A	Discussion of power was in original article and may not be relevant to this specific nested case control.	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kukuljan et al., 2009	RCT/CCT	51–70 years; Healthy; men; community-dwelling; Caucasian	had taken calcium and/or vitamin D supplements; Osteoporosis; used medication known to affect bone metabolism; medical condition known to affect bone metabolism, any chronic condition that might limit their ability to be involved in the intervention; current smoking; chronic condition that might limit ability to be involved in the intervention; lactose intolerance		Private Foundation	Australia;Victoria	180/85/0	59.9 (7.4)/50–79	Non-Hispanic White=100		serum 25(OH)D 86.2 ± 35.9 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Kukuljan et al., 2009	RCT/CCT	NR	NR	Secondary-Step Test	Ca & Vit D3 fortified milk lg & 800 IU daily		43	9.90 (SD=2.9)	final=11.4 (SD=3.00)	-6 (-2.0, 0.75)	0.38
					Control		42	10.30 (SD=2.8)	final=12.0 (SD=3.30)	.	
				Secondary-Gait Speed	Ca & Vit D3 fortified milk lg & 800 IU daily		43	2.84 (SD=0.96)	final=2.79 (SD=1.17)	+0.13 (-0.36, 0.62)	0.6
					Control		42	3.08 (SD=1.36)	final=2.66 (SD=1.12)	.	
				Secondary-Sway, Eyes Open, On Floor	Ca & Vit D3 fortified milk lg & 800 IU daily		43	294.00 (SD=282)	final=326 (SD=344)	+147 (32.4, 261.6)	0.01
					Control		42	320.00 (SD=366)	final=179 (SD=147)	.	
				Secondary-Sway, Eyes Closed, On Floor	Ca & Vit D3 fortified milk lg & 800 IU daily		43	364.00 (SD=318)	final=241 (SD=192)	-79 (-207, 49)	0.22
					Control		42	285.00 (SD=232)	final=320 (SD=373)	.	
				Secondary-Sway, Eyes Open, On Foam	Ca & Vit D3 fortified milk lg & 800 IU daily		43	737.00 (SD=762)	final=596 (SD=733)	+248 (9, 487)	0.04
					Control		42	597.00 (SD=532)	final=348 (SD=266)	.	
				Secondary-Sway, Eyes Closed, On Foam	Ca & Vit D3 fortified milk lg & 800 IU daily		43	1317.00 (SD=875)	final=1045 (SD=787)	-209 (-721, 303)	0.42
					Control		42	1437.00 (SD=1217)	final=1254 (SD=1489)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Kukuljan et al., 2009	RCT/CCT	ND	ND	Y	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kukuljan et al., 2011	RCT/CCT	19–50 years; 51–70 years; Healthy; male; normal to below average BMD; community dwelling; Caucasian	use of calcium-vitamin D supplementation within the past 12 months; Prior fragility fracture; chronic condition that might limit participation in the trials; participation in resistance training; BMI >35kg/m2; lactose intolerance; any medical conditions or medication use known to affect bone metabolism; current smoker		Manufacturer	Australia; Geelong	180/89/0	59.9 (7.4)/NR	Non-Hispanic White=100		calcium intake: 911–1064 mg/d Serum vitamin D level: 34.5+/-14.4 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Kukuljan et al., 2011	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Changes In Weight	Secondary-L1-L3 Total Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	164 (sd=25)	change=-0.6 (-2.1, 0.8)	-0.6 (-2.7, 1.6)	.
					D3 controls		44	171 (sd=34)	change=-0.05 (-1.5, 1.4)		.
				Secondary-L1-L3 Trabecular Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	115 (sd=22)	change=-1.5 (-3.1, 0.9)	-2.3 (-6.4, 1.8)	.
					D3 controls		44	120 (sd=34)	change=0.8 (-2.9, 1.2)		.
				Secondary-Mid-Femur Cortical Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	1104 (sd=39)	change=-1.0 (-1.4, -0.6)	-0.3 (-1.0, 0.4)	.
					D3 controls		44	1108 (sd=38)	change=-0.7 (-1.3, -0.2)		.
				Secondary-Mid-Tibia Cortical Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	1105 (sd=43)	change=-1.2 (-1.7, -0.7)	-0.1 (-0.8, 0.6)	.
					D3 controls		44	1113 (sd=49)	change=-1.1 (-1.6, -0.5)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Kukuljan et al., 2011	RCT/CCT	Y	ND	Y	Y	ND	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Laaksi et al., 2010	RCT/CCT	19–50 years; 18–28 years; no regular medication; passed the entry medical examination as healthy	use of supplementary vitamin D, multivitamins and cod liver oil		Government	Finland; Pori Brigade	164/328/0	NR/NR			Serum vitamin D level: intervention group- 78.7+/- TM 14.9 nmol/L placebo- 74.4 TM +/-20.8 nmol/L	

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Laaksi et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Smoking	Primary-Self Reported Common Cold Symptoms	Vit D3	400 IU	6 months	45/80	Crude/OR	1.17	0.63, 2.16	0.619
					Placebo	Placebo	6 months	44/84	Crude/OR	1	reference	
				Primary-No Days Absent From Duty	Vit D3	400 IU	6 months	41/80	Crude/OR	1.89	1.01, 3.54	0.045
					Placebo	Placebo	6 months	30/84	Crude/OR	1	reference	

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Laaksi et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Smoking	Secondary-Days Absent From Duty	Vit D3 400 IU		80	NR (NR)	final=2.2 (SD=3.2)	-0.8 (-1.9, 0.3)	0.096
					Placebo		84	NR (NR)	final=3.0 (SD=4.0)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Laaksi et al., 2010	RCT/CCT	Y	ND	Y	N	Y	Y	N	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Lee et al., 2011	Nested Case Control	19–50 years; 51–70 years; U.S. male physicians; 40–84 years	vitamin A or beta carotene; cancer except non melanoma skin cancer; myocardial infarction, stroke, or transient ischemic attack; renal or liver disease; peptic ulcer; gout	Physicians' Health Study	Government	USA; multiple	618/618/0	NR/NR			NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Lee et al., 2011	Nested Case Control	NR	Other Nutrients Or Dietary Factors- Fasting Status, Dairy Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI; Sun Exposure- Seasons; Smoking, Other Lifestyle Factors- Smoking Status, Vigorous Exercise	Primary-Colorectal Cancer	25(OH)D	Quartile 1 (median 15.7ng/mL)	NR	57/153	adjusted/OR	1	reference	
					25(OH)D	Quartile 2 (median 22.3ng/mL)	NR	41/138	adjusted/OR	0.71	0.42, 1.21	
					25(OH)D	Quartile 3 (median 26.7ng/mL)	NR	74/173	adjusted/OR	1.24	0.76, 2.04	
					25(OH)D	Quartile 4 (median 37.9ng/mL)	NR	57/154	adjusted/OR	1.08	0.62, 1.87	0.670
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	66/159	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	60/156	adjusted/OR	0.91	0.55, 1.50	
				Primary-Colon Cancer	1,25(OH)2D	Quartile 3 (median 34.7pg/mL)	NR	53/149	adjusted/OR	0.84	0.51, 1.38	
					1,25(OH)2D	Quartile 4 (median 41.1pg/mL)	NR	45/139	adjusted/OR	0.7	0.41, 1.18	0.240
					25(OH)D	Quartile 1 (median 15.7ng/mL)	NR	36/106	adjusted/OR	1	reference	
					25(OH)D	Quartile 2 (median 22.3ng/mL)	NR	37/109	adjusted/OR	0.95	0.52, 1.74	
					25(OH)D	Quartile 3 (median 26.7ng/mL)	NR	52/126	adjusted/OR	1.34	0.75, 2.39	
					25(OH)D	Quartile 4 (median 37.9ng/mL)	NR	47/118	adjusted/OR	1.38	0.73, 2.64	0.350
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	49/117	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	40/111	adjusted/OR	0.83	0.46, 1.49	
					1,25(OH)2D	Quartile 3 (median 34.7pg/mL)	NR	47/118	adjusted/OR	0.96	0.54, 1.68	
					1,25(OH)2D	Quartile 4 (median 41.1pg/mL)	NR	33/104	adjusted/OR	0.64	0.34, 1.19	0.220

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
				Primary-Rectal Cancer	25(OH)D	Quartile 1 (median 15.7ng/mL)	NR	20/44	adjusted/OR	1	reference	
					25(OH)D	Quartile 2 (median 22.3ng/mL)	NR	15/41	adjusted/OR	0.53	0.18, 1.60	
					25(OH)D	Quartile 3 (median 26.7ng/mL)	NR	9/37	adjusted/OR	0.42	0.13, 1.40	
					25(OH)D	Quartile 4 (median 37.9ng/mL)	NR	13/37	adjusted/OR	0.45	0.14, 1.46	0.050
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	20/44	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	13/37	adjusted/OR	0.57	0.20, 1.60	
					1,25(OH)2D	Quartile 3 (median 34.7pg/mL)	NR	10/36	adjusted/OR	0.43	0.13, 1.39	
					1,25(OH)2D	Quartile 4 (median 41.1pg/mL)	NR	12/36	adjusted/OR	0.75	0.27, 2.09	0.720

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Lee et al., 2011	Y	N	Y	Y						N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Lin et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Healthy; 40–69 years	death before start of intervention		Government	China; Linxian	1101/1101/45	56.5 (7.9)/NR	Asian=100	Other; hypertension 27%	254 had serum vitamin D<19.6 nmol/L 278 had serum D of 19.6–31.8 nmol/L 262 had serum D of 31.9–48.3 nmol/L 307 had serum D of =48.4 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Lin et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Medical Conditions- Hypertension; Smoking, Other Lifestyle Factors- Tobacco Smoking, Alcohol	Primary-All-Cause Mortality	25(OH)D	continuous 25(OH)D	24 yrs	793/1101	adjusted/HR	1.01	0.97, 1.05	0.735
					25(OH)D	continuous 25(OH)D-men	24 yrs	479/608	adjusted/HR	0.99	0.94, 1.04	0.7
					25(OH)D	continuous 25(OH)D-women	24 yrs	314/493	adjusted/HR	1.03	0.97, 1.10	0.348
				Primary-Cancer Deaths	25(OH)D	continuous 25(OH)D	24 yrs	217/1101	adjusted/HR	0.97	0.89, 1.05	0.406
					25(OH)D	continuous 25(OH)D-men	24 yrs	141/608	adjusted/HR	1	0.91, 1.10	0.967
					25(OH)D	continuous 25(OH)D-women	24 yrs	76/493	adjusted/HR	0.88	0.75, 1.03	0.115
				Primary-Cerebrovascular Death	25(OH)D	continuous 25(OH)D	24 yrs	279/1101	adjusted/HR	1.05	0.98, 1.12	0.141
					25(OH)D	continuous 25(OH)D-men	24 yrs	157/608	adjusted/HR	1.04	0.96, 1.13	0.337
					25(OH)D	continuous 25(OH)D-women	24 yrs	122/493	adjusted/HR	1.06	0.96, 1.17	0.277
				Primary-Cardiovascular Death	25(OH)D	continuous 25(OH)D	24 yrs	200/1101	adjusted/HR	0.98	0.91, 1.06	0.678
					25(OH)D	continuous 25(OH)D-men	24 yrs	119/608	adjusted/HR	0.94	0.85, 1.04	0.223
					25(OH)D	continuous 25(OH)D-women	24 yrs	81/493	adjusted/HR	1.06	0.93, 1.20	0.399

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Lin et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	N	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Lips et al., 2010	RCT/CCT	ambulatory; mentally competent; If patients had serum 25(OH)D concentrations = 6 but = 9ng/mL; men and women	Current cancer; treatment with > or equal to .800 IU vitamin D/d or with active metabolites of vitamin D within 6 mo of screening; or treatment with any drug that might affect vitamin D metabolism or interfere with postural stability		Manufacturer	USA; 9 centers; Multiple Countries; Europe- 3 centers	213/213/NR	77.6 (6.6)/NR			serum vitamin D- placebo- 14.1+/-5.5 ng/ml, D3- 13.7+/-4.4 ng/ml serum calcium-placebo- 9.4+/-0.4mg/dl, D3- 9.4+/-0.4mg/dl

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Lips et al., 2010	RCT/CCT	NR	NR	Secondary-Short Physical Performance Battery (SPPB) Summary Score	Vit D3 8,400 IU/weekly		109	9.00 (SD=2.3)	change= 0.355 (0.108, 0.601)	-0.25 (-0.60, -0.10)	0.17
					Placebo		104	9.07 (SD=2.0)	change= 0.601 (0.351, 0.852)	reference (NR)	.
				Secondary-Short Physical Performance Battery (SPPB) Gait Speed	Vit D3 8,400 IU/weekly		109	93.70 (SD=31.5)	change= 3.10 (-0.252, 6.458)	-0.84 (-5.63, 3.95)	0.73
					Placebo		104	88.70 (SD=25.9)	change= 3.94 (0.567, 7.38)	reference (NR)	.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Lips et al., 2010	RCT/CCT	Y	ND	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Looker et al., 2013	Prospective Cohort	51–70 years; >=65 years	prior fracture; ineligible for linkage to the Medicare denominator file; enrolled in a HMO	NHANES III	Government	USA; multiple	4749/4749/74.3	75.2 (NR)/NR	Non-Hispanic White=925; Non-Hispanic Black=37; Race_other1=17; Race_other2=21	Not Reported	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Looker et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race	Primary-Major Osteoporotic Fracture	25(OH)D	per 1 SD unit decline in serum 25OHD	7 yrs	400/4749	adjusted/RR	1.27	1.12, 1.44	
					25(OH)D	per 1 SD unit decline in serum 25OHD-65-79	7 yrs	212/NR	adjusted/RR	1.14	0.97, 1.34	
					25(OH)D	per 1 SD unit decline in serum 25OHD->=80	7 yrs	188/NR	adjusted/RR	1.4	1.13, 1.74	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Looker et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	reconciled

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Macdonald et al., 2013	RCT/CCT	51–70 years; Postmenopausal women; Healthy; 60–70 years of age; non-smoking	Type 2 DM; asthma; malabsorption; abnormal biochemical profile; blood pressure>160mm Hg systolic or >99 mm Hg diastolic; use of corticosteroids, anti-inflammatories, hypotensive, hypolipemic; unstable thyroid function; planned trips that would result in increased UV light exposure	Vitamin D and Cardiovascular Risk [VICTORY]	university	UK; Scotland	264/259/100	64.6 (2.3)/NR		Post menopausal	35.8±16.4 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Macdonald et al., 2013	RCT/CCT	Not relevant	Other Nutrients Or Dietary Factors- Calcium Intake; Smoking, Other Lifestyle Factors- Physical Activity	Secondary-Total Hip BMD	D3 400 IU		83	0.917 (sd=0.102)	final=0.912 (sd=0.103)	-0.002 (-0.036, 0.032)	0.91
					D3 1000 IU		88	0.923 (sd=0.132)	final=0.923 (sd=0.135)	+0.009 (-0.029, 0.047)	0.64
					placebo		88	0.92 (sd=0.118)	final=0.914 (sd=0.118)		.
				Secondary-Total Lumbar Spine BMD	D3 400 IU		83	1.075 (sd=0.141)	final=1.076 (sd=0.135)	+0.006 (-0.038, 0.050)	0.79
					D3 1000 IU		88	1.068 (sd=0.161)	final=1.071 (sd=0.164)	+0.001 (-0.046, 0.048)	0.97
					placebo		88	1.081 (sd=0.153)	final=1.070 (sd=0.153)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Macdonald et al., 2013	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Magnus et al., 2013	Nested Case Control	Pregnant or lactating women; approximately 18 weeks gestation	Not specified	Norwegian Mother and Child Cohort Study	Private Foundation	Norway	1,248/1672/100	NR (NR)/NR			NR	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Magnus et al., 2013	Nested Case Control	unclear	Other Nutrients Or Dietary Factors- Maternal Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Maternal Age At Pregnancy, Education; Anthropometrics- Prepregnancy BMI; Medical Conditions- Maternal History Of Asthma; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Asthma	25(OH)D	20 nmol/L increase in 25(OH)D	36 mos	489/1672	adjusted/OR	0.91	0.81, 1.02	
					25(OH)D	<51	36 mos	114/316	adjusted/OR	1	Reference	
					25(OH)D	51–75	36 mos	187/584	adjusted/OR	0.84	0.61, 1.17	
					25(OH)D	>75	36 mos	188/771	adjusted/OR	0.67	0.48, 0.95	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Magnus et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Mai et al., 2012	Nested Case Control	19–50 years; 51–70 years; 19 years or older; of Nord-Trondelag; 65 years or less	Not specified	HUNT study	Manufacturer	Nord-Trondelag, Norway	2613/2542/57	39.7 (8.5)/NR		Not Reported	women cases- 56.7 (23.7) nmol/L, controls- 59.5 (23.1) nmol/L men cases- 54.8 (20.8) nmol/L, controls- 58.9 (23.5) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Mai et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Daily Smoking, Physical Activity; Other - Allergic Rhinitis, Copd, Social Benefit, Economic Difficulties	Primary-Asthma	25(OH)D	>=75.0-female	11 yrs	81/328	adjusted/OR	1	Reference	
					25(OH)D	50.0–74.9-female	11 yrs	125/555	adjusted/OR	0.8	0.57, 1.13	
					25(OH)D	<50.0-female	11 yrs	170/566	adjusted/OR	0.94	0.67, 1.32	
					25(OH)D	each 25-nmol/L reduction-female	11 yrs	376/1449	adjusted/OR	0.97	0.85, 1.12	
					25(OH)D	>=75.0-male	11 yrs	33/247	adjusted/OR	1	Reference	
					25(OH)D	50.0–74.9-male	11 yrs	77/384	adjusted/OR	1.5	0.95, 2.38	
					25(OH)D	<50.0-male	11 yrs	98/462	adjusted/OR	1.47	0.93, 2.32	
					25(OH)D	each 25-nmol/L reduction-male	11 yrs	208/1093	adjusted/OR	1.14	0.94, 1.37	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Mai et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
McCullough et al., 2009	Nested Case Control	Not specified	pre or perimenopausal at baseline; no appropriate match; one or less vials of serum; extreme 25(OH)D level	Cancer Prevention Study-II (CPS-II)	Unclear	USA; 21 states	1032/1032/100	69.6 (5.8)/NR	Non-Hispanic White=971; Race_other1=29		Plasma 25(OH)D cases- 56.5 (22.0) nmol/L controls- 56.2 (22.2) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
McCullough et al., 2009	Nested Case Control	race, ethnicity, date of blood draw	Demographics (Age, Sex, Race/Ethnicity)- Birth Year, Race; Anthropometrics- Body Mass Index At Blood Collection, Weight Change From Age 18 Years To Blood Collection; Sun Exposure- Season; Other - Parity And Age At First Birth	Primary-Breast Cancer	25(OH)D	<36.7nmol/L	1month–6.9years	89/193	adjusted/OR	1	reference	
					25(OH)D	36.7<49.8nmol/L	1month–6.9years	115/217	adjusted/OR	1.29	0.86, 1.94	
					25(OH)D	49.8<60.8nmol/L	1month–6.9years	99/204	adjusted/OR	1.14	0.75, 1.72	
					25(OH)D	60.8<73.2nmol/L	1month–6.9years	118/220	adjusted/OR	1.44	0.96, 2.18	
					25(OH)D	>73.2nmol/L	1month–6.9years	95/198	adjusted/OR	1.09	0.70, 1.68	0.600

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
McCullough et al., 2009	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Reconciled In the 2009 report: Population b) Y=random or consecutive, N=other sampling like convenience; Outcome c) NA for all observational studies. If we followed this, then this article would have grade A.

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Mena et al., 2013	Prospective Cohort	50–74 years of age between 2000 and 2002	Prior cancer; Current cancer; diagnosis of any type of cancer prior to baseline	Esther	Government	Germany (specify city, if given); Saarland	9,580/9007/46	NR (NR)/50–74			reported by season for each quartile

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Mena et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors-; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- Obesity; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Family History Of Cancer	Primary-Total Cancer	25(OH)D	Q1	8 yrs	235/2253	adjusted/HR	1.1	0.93, 1.30	
					25(OH)D	Q2+Q3	8 yrs	396/4500	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	242/2254	adjusted/HR	1.12	0.95, 1.32	
				Primary-Prostate Cancer	25(OH)D	Q1	8 yrs	38/882	adjusted/HR	1.16	0.78, 1.74	
					25(OH)D	Q2+Q3	8 yrs	66/1737	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	67/1505	adjusted/HR	1.21	0.86, 1.70	
				Primary-Breast Cancer	25(OH)D	Q1	8 yrs	38/1464	adjusted/HR	1.08	0.72, 1.60	
					25(OH)D	Q2+Q3	8 yrs	71/2951	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	28/846	adjusted/HR	1.39	0.89, 2.18	
				Primary-Colorectal Cancer	25(OH)D	Q1	8 yrs	37/2373	adjusted/HR	1.02	0.68, 1.53	
					25(OH)D	Q2+Q3	8 yrs	69/4741	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	30/2368	adjusted/HR	0.77	0.50, 1.20	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Mena et al., 2013	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Menant et al., 2012	Prospective Cohort	70–90 years; independent in ADLs = activities of daily living; able to walk 400m without assistance; community dwelling	multiple sclerosis; medical or psychological conditions that may prevent them from completing assessments; dementia or developmental disability; psychotic symptoms; Parkinson's disease; motor neuron disease; CNS inflammation	Memory and Ageing Study	Government	Australia; Sydney	463/926/54	78 (4.6)/70–90			serum vitamin D- 62.2±24.6 nmol/L;

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Menant et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI	Primary-Falls In Men	25(OH)D	>= 50nmol/l	1 y	94/215	Crude/IRR	1.93	1.19, 3.15	0.008
					25(OH)D	> 50nmol/l	1y		Crude/IRR	1	Reference	
				Primary-Falls In Women	25(OH)D	>= 50nmol/l	1 y	115/248	Crude/IRR	0.83	0.56, 1.23	0.362
					25(OH)D	> 50nmol/l	1 y		Crude/IRR	1	Reference	

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Menant et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI	Secondary-Grip Strength	25(OH)D > 50 nmol/l		309	NR (NR)	final= 28.7 (SD=11.7)	+4.7 (3.3, 6.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 24.0 (SD=10.3)		.
				Secondary-Quadriceps Strength	25(OH)D > 50 nmol/l		309	NR (NR)	final= 28.9 (SD=11.9)	+6 (5, 7)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 22.9 (SD=10.4)		.
				Secondary-Finger Press Reaction Time	25(OH)D > 50 nmol/l		309	NR (NR)	final= 235.4 (SD=45.2)	-11.7 (NR)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 247.1 (SD=50.0)		.
				Secondary-Sway, Eyes Open-Floor	25(OH)D > 50 nmol/l		309	NR (NR)	final= 76.5 (SD=40.1)	-5.4 (-11.0, 0.2)	0.06
					25(OH)D = 50nmol/l		154	NR (NR)	final= 81.9 (SD=46.0)		.
				Secondary-Sway, Eyes Open-Foam	25(OH)D > 50 nmol/l		309	NR (NR)	final= 182.2 (SD=97.5)	-5.6 (-17.7, 6.5)	0.37
					25(OH)D = 50nmol/l		154	NR (NR)	final= 187.8 (SD=89.9)		.
				Secondary-Physiological Profile Assessment (PPA) Fall Risk Score	25(OH)D > 50 nmol/l		309	NR (NR)	final= 0.8 (SD=0.9)	-0.2 (-0.3, -0.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 1.0 (SD=0.9)		.
				Secondary-Maximal Balance Range	25(OH)D > 50 nmol/l		309	NR (NR)	final= 155.7 (SD=56.8)	+21.1 (14.2, 28.0)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 134.6 (SD=49.7)		.
				Secondary-Coordinated Stability Score	25(OH)D > 50 nmol/l		309	NR (NR)	final= 13.6 (SD=12.4)	-5.0 (-7, -3)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 18.6 (SD=13.3)		.
				Secondary-Choice Stepping Reaction Time	25(OH)D > 50 nmol/l		309	NR (NR)	final= 987.4 (SD=215.1)	-73.4 (-101.7, -45.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 1060.8 (SD=223.0)		.

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-6 M Walk Speed	25(OH)D > 50 nmol/l		309	NR (NR)	final= 0.73 (SD=0.16)	+0.06 (0.04, 0.08)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 0.67 (SD=0.17)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Supplement Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Menant et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Messenger et al., 2012	Prospective Cohort	51–70 years; 65 and older; men	inability to walk without assistance from another person; bilateral hip replacements; inability to provide self-reported data	Osteoporotic Fractures in Men Sleep Study MrOS	Government	USA; multiple	813/813/0	76.1 (5.6)/NR	Non-Hispanic White=91		quartiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Messenger et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race, Sex; Anthropometrics- BMI; Medical Conditions- History Of Hypertension, Diabetes, And CV Event; Smoking, Other Lifestyle Factors- Smoking, Alcohol Use; Other - Diastolic BP, PASE Score, Statin Use, HDL, LDL, Triglycerides, Glucose, Insulin, Site And Season	Primary- Cardiovascular Disease(CHD & CVA)	25(OH)D	4.8–20.1 ng/ml	4.4 yrs (median)	39/204	Adjusted/HR	1.18	0.69, 2.03	0.85
					25(OH)D	20.2–25.2 ng/ml	4.4 yrs (median)	33/203	Adjusted/HR	1.11	0.65, 1.91	
					25(OH)D	25.3–30.0 ng/ml	4.4 yrs (median)	35/202	Adjusted/HR	0.97	0.57, 1.64	
					25(OH)D	30.1–55.4 ng/ml	4.4 yrs (median)	33/204	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Messenger et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Meyer et al., 2013	Nested Case Control	cases: new cases of prostate cancer; cases: donated serum>=1yr before diagnosis; Not specified	Prior cancer; controls: alive and free from cancer; missing data		Manufacturer	Norway- 17 of 19 counties	4212/4212/0	48.2 (9.2)/NR			serum vitamin D: cases- 64.4+/-22.2 nmol/L, controls- 62.4+/-22.3 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Meyer et al., 2013	Nested Case Control	age at serum sampling, date of serum sampling, county of residence	Demographics (Age, Sex, Race/Ethnicity)- Education; Sun Exposure- Month	Primary-Prostate Cancer	25(OH)D	<30nmol/L	NR	72/164	adjusted/RR	0.82	0.58, 1.15	
					25(OH)D	30–49nmol/L	NR	528/1081	adjusted/RR	1.02	0.87, 1.21	
					25(OH)D	50–69nmol/L	NR	718/1489	adjusted/RR	1	reference	
					25(OH)D	70–89nmol/L	NR	537/1003	adjusted/RR	1.24	1.05, 1.47	
					25(OH)D	≥90nmol/L	NR	251/475	adjusted/RR	1.17	0.93, 1.48	
					25(OH)D	30-nmol/L increase	NR	NR/4212	adjusted/RR	1.13	1.02, 1.25	
					25(OH)D	<30nmol/L-Winter and Spring	NR	49/112	adjusted/RR	0.8	0.52, 1.23	
					25(OH)D	30–49nmol/L-Winter and Spring	NR	304/590	adjusted/RR	1.09	0.86, 1.40	
					25(OH)D	50–69nmol/L-Winter and Spring	NR	288/585	adjusted/RR	1	reference	
					25(OH)D	70–89nmol/L-Winter and Spring	NR	145/273	adjusted/RR	1.14	0.85, 1.53	
					25(OH)D	≥90nmol/L-Winter and Spring	NR	38/88	adjusted/RR	0.74	0.46, 1.18	
					25(OH)D	30-nmol/L increase-Winter and Spring	NR	NR/1648	adjusted/RR	0.97	0.83, 1.14	
					25(OH)D	<30nmol/L-Summer and Autumn	NR	13/27	adjusted/RR	0.97	0.45, 2.10	
					25(OH)D	30–49nmol/L-Summer and Autumn	NR	132/304	adjusted/RR	0.87	0.66, 1.16	
					25(OH)D	50–69nmol/L-Summer and Autumn	NR	296/625	adjusted/RR	1	reference	
					25(OH)D	70–89nmol/L-Summer and Autumn	NR	297/625	adjusted/RR	1.34	1.05, 1.71	
					25(OH)D	≥90nmol/L-Summer and Autumn	NR	180/324	adjusted/RR	1.46	1.07, 2.00	
					25(OH)D	30-nmol/L increase-Summer and Autumn	NR	NR/1905	adjusted/RR	1.25	1.08, 1.45	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Meyer et al., 2013	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	N	Y	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Michael et al., 2011	Prospective Cohort	51–70 years; 65–79 years	Not specified	WHI CT	Government	USA ;multiple	534/534/100	70.3 (3.7)/50–79	Non-Hispanic White=92; Hispanic=8; Race_other1=		serum vitamin D- 48.2+/- 21.4 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Michael et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race/Ethnicity; Anthropometrics- BMI; Medical Conditions- Chronic Conditions; Sun Exposure- Clinic Latitude, Season, Time Walked Outside; Other - DM Trial Arm	Primary-Physical Performance Summary Score	25(OH)D	>= 75 nmol/l	6 y	NR/64	Adjusted/RR	3.66	1.88, 5.45	<0.001
					25(OH)D	50–74nmol/l	6 y	NR/148	Adjusted/RR	2.32	0.89, 3.75	
					25(OH)D	25–49 nmol/l	6 y	NR/255	Adjusted/RR	1.64	0.28, 3.01	
					25(OH)D	>= 25 nmol/l	6 y	NR/67	Adjusted/RR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Michael et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	eligibility criteria not clear from this article but exclusion criteria were probably named in the original studies exposure a unclear

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Michaels son et al., 2010	Prospective Cohort	51–70 years; birth 1920–1924; Age approximately 71; male; Uppsala resident	Not specified	Uppsala Longitudinal Study of Adult Men	Swedish Research Council	Uppsala, Sweden	1,194/1194/0	71.0 (0.6)/NR		Other; more than 1/3 being treated for hypertension	For 10th–90th percentile: Mean Dietary Intake: 5.8ug/d(2.2) Mean total intake: 6.0ug/d (2.4) Plasma 25(OH)D: 46–93 nmol/L (18–37 ng/ml)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Michaels son et al., 2010	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Weight, Height; Medical Conditions- Hypertension, Type 2 Diabetes; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking Status; Other - Socioeconomic Status, Plasma PTH, Serum Calcium, Cystatin C, Serum Phosphate, Plasma Cholesterol, Self-Perceived Health	Primary-Overall Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	76/119	adjusted/HR	1.43	1.11, 1.84	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	444/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	64/119	adjusted/HR	1.27	0.97, 1.66	
				Primary-Cardiovascular Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	24/119	adjusted/HR	1.53	0.97, 2.41	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	135/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	18/119	adjusted/HR	1.16	0.69, 1.93	
				Primary-Cancer Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	27/119	adjusted/HR	1.99	1.29, 3.08	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	118/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	19/119	adjusted/HR	1.56	0.95, 2.56	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Michaels son et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B	didn't specify exclusion criteria	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Molgaard et al., 2010	RCT/CCT	9–18 years; girls; 11–12 years of age; Danish birth and citizenship	not specified; calcium or other vitamins or minerals; chronic diseases; intake of drugs that could influence bone metabolism		Government	Copenhagen and Frederiksberg Denmark	225/221/100	11.4 (0.2)/NR	Non-Hispanic White=100		Vitamin D intake: placebo-2.6±1.4ug/d Serum vitamin D level: placebo-43.4±17.1 nmol/L Calcium intake: placebo-955±588 mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Molgaard et al., 2010	RCT/CCT	age	Anthropometrics- Size - Bone And Body Size (The Outcome Is Adjusted Bone Mineral Content), Bone Area, Height, Weight; Other - Baseline Vitamin D, Tanner Stage, Vitamin D Receptor Genotype, Estrogen Receptor Genotype	Secondary-L1-L4 BMC	D3 10 µg Vit D3/day		74	28.9 (sd=6.4)	final=36.3 (sd=8.6)	-1.2 (-4.3, 1.9)	.
					D3 5 µg Vit D3/day		73	29.4 (sd=7.8)	final=37.6 (sd=10.3)	+0.1 (-3.2, 3.4)	.
					D3 placebo		74	29.2 (sd=7.7)	final=37.5 (sd=10.2)		.
				Secondary-L1-L4 BMD	D3 10 µg Vit D3/day		74	0.695 (sd=0.089)	final=0.780 (sd=0.113)	-0.01 (-0.05, 0.03)	.
					D3 5 µg Vit D3/day		73	0.698 (sd=0.092)	final=0.786 (sd=0.115)	-0.0 (-0.04, 0.04)	.
					D3 placebo		74	0.697 (sd=0.102)	final=0.788 (sd=0.121)		.
				Secondary-Whole Body BMD	D3 10 µg Vit D3/day		74	0.872 (sd=0.070)	final=0.917 (sd=0.080)	+0.01 (-0.02, 0.03)	.
					D3 5 µg Vit D3/day		73	0.866 (sd=0.066)	final=0.915 (sd=0.075)	+0.01 (-0.02, 0.03)	.
					D3 placebo		74	0.863 (sd=0.064)	final=0.909 (sd=0.075)		.
				Secondary-Whole Body BMC	D3 10 µg Vit D3/day		74	1308 (sd=303)	final=1561 (sd=366)	+38 (-74, 150)	.
					D3 5 µg Vit D3/day		73	1311 (sd=277)	final=1559 (sd=324)	+36 (-70, 142)	.
					D3 placebo		74	1277 (sd=273)	final=1523 (sd=324)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Molgaard et al., 2010	RCT/CCT	Y	ND	ND	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Moschos et al., 2010	RCT/CCT	51–70 years; Postmenopausal women; women; 55–65 years of age	Osteoporosis; Prior cancer; Current cancer; Current cardiovascular disease; Type 2 DM; thiazide diuretics, glucocorticoids,; calcium, vitamin D, magnesium, phosphorus; t-score<-2.5; any other degenerative chronic degenerative disease, e.g., nephrolithiasis, hyper- or hypothyroidism,, impaired liver or renal function; smoking; less than 1 year postmenopausal; abnormal values on hematologic and biochemical examinations; taking medications and/or dietary supplements that affect bone metabolism	Postmenopausal Health Study	Manufacturer	Greece	66/66/100	60.7 (5.0)/NR		Post menopausal	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level:26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Moschos et al., 2010	RCT/CCT	Not described	NR	Secondary-Pelvis BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.096 (sd=0.078)	final=1.089 (sd=0.087)	+0.02 (-0.02, 0.06)	.
					D3 control (neither counselling nor dietary products)		31	1.067 (sd=0.102)	final=1.067 (sd=0.084)		.
				Secondary-Total Body BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.134 (sd=0.072)	final=1.135 (sd=0.067)	+0.03 (-0.01, 0.06)	.
					D3 control (neither counselling nor dietary products)		31	1.124 (sd=0.083)	final=1.106 (sd=0.078)		.
				Secondary-Total Spine BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.119 (sd=0.124)	final=1.234 (sd=0.135)	+0.04 (-0.03, 0.11)	.
					D3 control (neither counselling nor dietary products)		31	1.139 (sd=0.152)	final=1.193 (sd=0.139)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Moschos et al., 2010	RCT/CCT	Y	ND	Y	Y	ND	N	ND	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Moschos et al., 2011	RCT/CCT	51–70 years; Postmenopausal women; Healthy; 55–65 years of age; self-dependent	Prior cancer; Current cancer; Current cardiovascular disease; Type 2 DM; e.g., thiazide diuretics, glucocorticoids; taking dietary supplements related to bone metabolism (calcium, magnesium, phosphorus, vitamin D); BMD T-score<-2.5; any bone degenerative chronic disease (nephrolithiasis, liver or kidney disease, cancer, hyper- or hypothyroidism, hyperparathyroidism; postmenopausal less than 1 year; taking medications or dietary supplements that affect bone metabolism; bone degenerative chronic disease; <1 year past menopause; smoking, osteoporosis, abnormal values on hematologic and biochemical examinations	Postmenopausal Health Study	Manufacturer	Greece	173/65/100	62.4 (5.3)/NR		Post menopausal	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Moschos et al., 2011	RCT/CCT	NR	NR	Secondary-Heel BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	0.476 (sd=0.091)	final=0.459 (sd=0.081)	-0.002 (-0.04, 0.04)	.
					D3 control		39	0.472 (sd=0.083)	final=0.461 (sd=0.083)		.
				Secondary-L2-L4 BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	1.121 (sd=0.158)	final=1.113 (sd=0.160)	+0.01 (-0.07, 0.10)	.
					D3 control		39	1.134 (sd=0.176)	final=1.101 (sd=0.167)		.
				Secondary-Total Body BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	1.112 (sd=0.077)	final=1.135 (sd=0.083)	+0.04 (0, 0.08)	.
					D3 control		39	1.095 (sd=0.079)	final=1.094 (sd=0.079)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Moschos et al., 2011	RCT/CCT	ND	ND	Y	Y	ND	N	ND	N	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Munger et al., 2013	Nested Case Control	Healthy; US Navy, MC active duty	Not specified		Government	USA	923/558/4.9	20.6 (4.0)/NR	Non-Hispanic White=607; Hispanic=126; Non-Hispanic Black=21; Not reported=54	Other; presumed healthy	Nested case control, so baseline vitamin D tertiles reported for cases and controls

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Munger et al., 2013	Nested Case Control	age, sex, race/ethnicity, dates of serum collection, and branch of active duty service (Navy or Marine Corps)	Sun Exposure- Latitudes Of State Of Residence Prior To Enlistment	Primary-Type 1 Diabetes Mellitus	25(OH)D	<75nmol/L-Cases with >=2 samples	5.4 years	45/102	Adjusted/RR	1	reference	
					25(OH)D	75-<100nmol/L-Cases with >=2 samples	5.4 years	76/236	Adjusted/RR	0.6	0.38, 0.97	
					25(OH)D	>=100nmol/L-Cases with >=2 samples	5.4 years	65/220	Adjusted/RR	0.56	0.35, 0.90	0.03

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Munger et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Murdoch et al., 2012	RCT/CCT	9–18 years; 19–50 years; 51–70 years; 18 years and older; staff or students of Canterbury District Health Board or University of Otago; able to give written informed consent; anticipating residence in Christchurch for the study period	Consumption of vitamin D supplements other than as part of a daily multi with a daily intake =400IU; Current cancer; Pregnant; history of hypercalcemia or nephrolithiasis; use of immuno-suppressants or medications that interfere with vitamin D metabolism (e.g., thiazide diuretics, phenytoin, carbamazepine, primidone, phenobarbital, prednisone>10mg/d, methotrexate, azathioprine, cyclosporine); sarcoidosis; kidney disorders requiring dialysis or polycystic kidney disease; cirrhosis; baseline plasma calcium corrected for albumin>10.4mg/dL or <8.4mg/dL; Enrollment or planned enrollment in other research study that would conflict with the present study; planned pregnancy during the study period	VIDARIS	Government	New Zealand	322/322/75	48 (10)/NR	Non-Hispanic White=93; Asian=3; Not reported=2; Race_other1=4; Race_other2=1	Not Reported	Serum vitamin D level:28±9 ng/ml Plasma calcium: 9.2±0.4 mg/dL

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Murdoch et al., 2012	RCT/CCT	NR	NR	Primary-Number of URTIs per Person	Vit D3 & Placebo	100,000IU-NR	18 months	3.7/161	Adjusted/RR	0.97	0.85,1.11	0.65
					Vit D3 & Placebo	Placebo-NR	18 months	3.7/161	Adjusted/RR	1	reference	
				Primary-No Of Days If Missed Work Per Episode	Vit D3 & Placebo	100,000IU-NR	18 months	0.76/161	Adjusted/RR	1.03	0.81, 1.30	0.82
					Vit D3 & Placebo	Placebo-NR	18 months	0.76/161	Adjusted/RR	1	reference	
				Primary-Duration Of Symptoms	Vit D3 & Placebo	100,000IU-NR	18 months	12/161	Adjusted/RR	0.96	0.73, 1.25	0.76
					Vit D3 & Placebo	Placebo-NR	18 months	12/161	Adjusted/RR	1	reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Murdoch et al., 2012	RCT/CCT	Y	ND	Y	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Neuhouser et al., 2012	Nested Case Control	Same as for CRC cohort	Same as for CRC cohort	Women's Health Initiative Calcium and Vitamin D Clinical Trial	Government	USA; multiple cities	2,160/2160/100	62.4 (6.9)/NR	Non-Hispanic White=783; Hispanic=36; Non-Hispanic Black=151; Not reported=30	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Neuhouser et al., 2012	Nested Case Control	NR	NR	Primary-Colorectal Cancer	25(OH)D	>=64.5nmol/L	NR	231/500	adjusted/OR	1	reference	
					25(OH)D	43.6<64.5nmol/L	NR	250/520	adjusted/OR	2.76	1.30, 5.89	
					25(OH)D	32.7<43.6nmol/L	NR	306/578	adjusted/OR	1.51	0.72, 3.14	
					25(OH)D	<32.7nmol/L	NR	293/562	adjusted/OR	4.45	1.96, 10.10 0.003	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Neuhouser et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	cancers confirmed by medical record review by health professionals	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Neuhouser et al., 2012	Nested Case Control	19–50 years; 51–70 years; Postmenopausal women; 50–79 years of age; If age=55, no menstrual period for at least 6 months; If age 50–54, no menstrual period for at least 12 months; life expectancy of at least 3 years	calcitriol or =600IU vitamin D per day; Hypertension; daily corticosteroids; any invasive cancer in prior 10 years, breast cancer at any time, suspicious mammography findings; MI in prior 6 months; stroke or TIA in prior 6 months; history of renal calculi or hypercalcemia; mental illness, dementia, alcohol or drug dependency; any medical condition with predicted survival < 3 years; chronic hepatitis, severe cirrhosis; severe underweight or anemia	WHI	Government	USA; multiple cities	620/620/100	65.1 (6.8)/NR	Non-Hispanic White=757; Hispanic=44; Non-Hispanic Black=171; Not reported=28	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Neuhouser et al., 2012	Nested Case Control	age, latitude of the clinical center (or clinical center location if latitude was not available), race/ethnicity, and blood collection date	Other Nutrients Or Dietary Factors- Vitamin D, Calcium, Red Meat Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI, Waist Circumference; Smoking, Other Lifestyle Factors- Smoking, Physical Activity, Alcohol Use; Other - Screening For CRC, Use Of Hormone Therapy	Primary-Breast Cancer	25(OH)D	>=64.9nmol/L	NR	53/130	adjusted/OR	1	reference	
					25(OH)D	50.9<64.9nmol/L	NR	84/162	adjusted/OR	0.99	0.75, 1.31	
					25(OH)D	36.7<50.9nmol/L	NR	68/147	adjusted/OR	1.11	0.83, 1.49	
					25(OH)D	<36.7nmol/L	NR	105/181	adjusted/OR	1.06	0.78, 1.43	0.600

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Neuhouser et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	cancers confirmed by medical record review by health professionals	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ng et al., 2009	RCT/CCT	19–50 years; 51–70 years; ambulatory; 18–80 years; stable medical condition; no change in medications for 6 months prior to study entry	Current cancer; Pregnant; current liver or kidney disorders; BMI >35 kg/m2; current tobacco use; h/o hypercalcemia, nephrolithiasis, sarcoidosis; recent hospitalization; malignancy and malabsorption; medications that interfere with vitamin D metabolism such as phenytoin and carbamazepine; use of immunosuppressants		Government	USA; Long Island, NY	162/296/79.7	58.1 (13.4)/NR	Non-Hispanic White=885; Non-Hispanic Black=41; Asian=54; Race_other1=20		The baseline 25-OHD levels ranged from 16 to 156 nmol/l with a mean level of 63.7+/-28.7 nmol/l in the study population. serum vitamin D: active- 64.3+/-5.4 nmol/L, placebo- 63.0+/-25.8 nmol/L calcium intake: active- 762.8+/-375.7 mg/d, placebo- 854.6+/-

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Ng et al., 2009	RCT/CCT	NR	NR	Primary-Upper Respiratory Tract	Vit D; IU/day	2000IU/day	12 weeks	28/78	Crude/OR	0.79	0.41, 1.54	0.61%
						Placebo	12 weeks	29/70	Crude/OR	1	reference	

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Ng et al., 2009	RCT/CCT	NR	NR	Secondary-Duration Of Upper Respiratory Tract	Vit D 2000IU/day		78	NR (NR)	final=5.4 (SD=4.8)	+1.0 (-1.2, 1.4)	0.86
					Placebo		70	NR (NR)	final=5.3 (SD=3.1)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Ng et al., 2009	RCT/CCT	Y	ND	ND	Y	Y	N	Y	ND	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Nieves et al., 2012	RCT/CCT	19–50 years; Postmenopausal women; women; Black; age over 45; natural spontaneous menopause or surgical ovariectomy at least 1 year prior to recruitment	Other systemic bone disease (e.g., Paget's); Current cancer; Current cardiovascular disease; Type 2 DM; Autoimmune disease; in the preceding 6 months; cardiac and pulmonary conditions; gastrointestinal, hepatic, and renal diseases; active hyperthyroidism; treatment with insulin, oral hypoglycemic agents, or thyroid hormone; smoking; drug abuse; rheumatoid arthritis		Government	USA; New York	127/103/100	61.2 (7.6)/NR	Non-Hispanic Black=100	Vitamin d deficient/depleted; Post menopausal	Serum 25(OH)D: 11.6±5.7 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Nieves et al., 2012	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI	Secondary-Femoral Neck BMD	D3 1,000 IU Vit D3		55	NR (NR)	change=-0.2 (NR)	+0.6 (NC)	.
					D3 placebo		48	NR (NR)	change=-0.8 (NR)		.
				Secondary-Spine BMD	D3 1,000 IU Vit D3		55	1.154 (sd=0.16)	change=-0.5 (NR)	+0.1 (NC)	.
					D3 placebo		48	1.212 (sd=0.15)	change=-0.6 (NR)		.
				Secondary-Total Hip BMD	D3 1,000 IU Vit D3		55	1.043 (sd=0.14)	change=-0.5 (NR)	+0.2 (NC)	.
					D3 placebo		48	1.04 (sd=0.13)	change=-0.7 (NR)		.
				Secondary-Trochanter BMD	D3 1,000 IU Vit D3		55	NR (NR)	change=-0.3 (NR)	+0.15 (NC)	.
					D3 placebo		48	NR (NR)	change=-0.45 (NR)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Nieves et al., 2012	RCT/CCT	ND	ND	ND	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Oeffelen et al., 2011	Prospective Cohort	3–8 years; newborns of mothers visiting prenatal clinics assessed at 4- and 8-years of age	Not specified	Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study	Government	The Netherlands	3963/862/48.1	NR/NR		Not Reported		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Oeffelen et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Gender; Smoking, Other Lifestyle Factors- Smoking In The House At 3 Months Of Age	Primary-Bronchial Hyperresponsiveness	25(OH)D	Tertile 1: range 23.1–60.2 nm	8 yrs	80/204	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	8 yrs	88/209	adjusted/OR	1.16	0.62, 2.18	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	8 yrs	87/194	adjusted/OR	1.19	0.63, 2.23	
				Primary-Atopy	25(OH)D	Tertile 1: range 23.1–60.2 nm	8 yrs	93/346	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	8 yrs	101/237	adjusted/OR	2.19	1.17, 4.12	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	8 yrs	93/279	adjusted/OR	1.23	0.64, 2.39	
				Primary-Asthma	25(OH)D	Tertile 1: range 23.1–60.2 nm	5–8 yrs	NR/NR	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.97	0.57, 1.65	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.68	0.39, 1.19	
				Primary-Severe Asthma	25(OH)D	Tertile 1: range 23.1–60.2 nm	5–8 yrs	NR/NR	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	5–8 yrs	NR/NR	adjusted/OR	1.06	0.59, 1.90	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.61	0.32, 1.15	

Quality of Cohort or Nested Case-Control Studies											
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)	
Oeffelen et al., 2011	Y	Y	N	Y				Y	Y	Y	

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Park et al., 2010	Nested Case Control	19–50 years; 51–70 years; men; 45–75 years of age; living in Hawaii or California	Not specified	Multiethnic Cohort Study	Government	USA; CA and HI	985/985/0	68.7 (7.2)/NR	Non-Hispanic White=166; Hispanic=159; Non-Hispanic Black=415; Race_other1=35; Race_other2=226	Not Reported	Serum vitamin D level:33.1±15.5 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Park et al., 2010	Nested Case Control	age at blood draw, fasting hours, season of blood draw	Other Nutrients Or Dietary Factors- Calcium Intake; Vitamin D Intake; Anthropometrics- BMI; Other - Physical Activity Level, Family History Of Prostate Cancer	Primary-Prostate Cancer	25(OH)D	Q1:<22.9ng/mL	NR	82/245	adjusted/OR	1	reference	
					25(OH)D	Q2: 22.9<31.0ng/mL	NR	84/250	adjusted/OR	1.05	0.70, 1.58	
					25(OH)D	Q3: 31.0<39.9ng/mL	NR	72/244	adjusted/OR	0.81	0.52, 1.28	0.470
					25(OH)D	Q4: >=39.9ng/mL	NR	91/246	adjusted/OR	1.17	0.72, 1.89	0.600
					25(OH)D	Deficient: <20ng/mL	NR	53/159	adjusted/OR	1.1	0.68, 1.78	
					25(OH)D	Insufficient: 20<30ng/mL	NR	98/302	adjusted/OR	1.04	0.73, 1.48	
					25(OH)D	30<50ng/mL	NR	137/424	adjusted/OR	1	reference	0.170
					25(OH)D	>=50ng/mL	NR	41/100	adjusted/OR	1.52	0.92, 2.51	0.320

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Park et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	No exclusion criteria listed or anything about how many people actually received the survey and how they were chosen...	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Perna et al., 2013	Prospective Cohort	19–50 years; 51–70 years; residence in the state of Saarland; sufficient knowledge of the German; age 50–74 years	history of CVD; unknown history of CVD; missing baseline measurements of 25(OH)D	ESTHER	Government	Germany (specify city, if given);Saarland	7709/7709/59.3	NR/50–74		Other; 46.3% hypertension	14.5% of population had serum D of <30 nmol/L, 44.5%- 31–<50 nmol/L, 41.1% >= 50 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Perna et al., 2013	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Regular Multivitamin Supplement Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Medical Conditions- Hypertension, DM, CKD; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - CRP, Family History Of CVD, Fish Consumption	Primary-Total Cvd	25(OH)D	< 30	6.5 yrs	171/1114	adjusted/HR	1.24	1.02, 1.50	
					25(OH)D	30—<50	6.5 yrs	448/3430	adjusted/HR	1.14	0.99, 1.32	
					25(OH)D	>=50	6.5 yrs	392/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	1011/7709	adjusted/HR	0.95	0.89, 1.01	
				Primary-Nonfatal Cvd	25(OH)D	< 30	6.5 yrs	136/1114	adjusted/HR	1.17	0.94, 1.45	
					25(OH)D	30—<50	6.5 yrs	383/3430	adjusted/HR	1.15	0.98, 1.35	
					25(OH)D	>=50	6.5 yrs	335/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	854/7709	adjusted/HR	0.98	0.91, 1.05	
				Primary-Fatal Cvd	25(OH)D	< 30	6.5 yrs	40/1114	adjusted/HR	1.55	1.01, 2.37	
					25(OH)D	30—<50	6.5 yrs	71/3430	adjusted/HR	1.05	0.73, 1.49	
					25(OH)D	>=50	6.5 yrs	65/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	176/7709	adjusted/HR	0.89	0.66, 0.94	
				Primary-Total Chd	25(OH)D	< 30	6.5 yrs	92/1114	adjusted/HR	1.32	1.02, 1.72	
					25(OH)D	30—<50	6.5 yrs	236/3430	adjusted/HR	1.19	0.98, 1.45	
					25(OH)D	>=50	6.5 yrs	208/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	536/7709	adjusted/HR	0.92	0.84, 1.01	
				Primary-Nonfatal Chd	25(OH)D	< 30	6.5 yrs	77/1114	adjusted/HR	1.28	0.97, 1.71	
					25(OH)D	30—<50	6.5 yrs	204/3430	adjusted/HR	1.18	0.95, 1.46	
					25(OH)D	>=50	6.5 yrs	179/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	460/7709	adjusted/HR	0.96	0.88, 1.06	
				Primary-Fatal Chd	25(OH)D	< 30	6.5 yrs	16/1114	adjusted/HR	1.53	0.80, 2.94	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
				Primary-Total Stroke	25(OH)D	30—<50	6.5 yrs	32/3430	adjusted/HR	1.18	0.70, 1.99	
					25(OH)D	>=50	6.5 yrs	31/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	79/7709	adjusted/HR	0.7	0.54, 0.93	
					25(OH)D	< 30	6.5 yrs	64/1114	adjusted/HR	1.31	0.95, 1.81	
					25(OH)D	30—<50	6.5 yrs	165/3430	adjusted/HR	1.2	0.94, 1.54	
					25(OH)D	>=50	6.5 yrs	124/3165	adjusted/HR	1	reference	
				Primary-Nonfatal Stroke	25(OH)D	per 25	6.5 yrs	353/7709	adjusted/HR	0.91	0.81, 1.02	
					25(OH)D	< 30	6.5 yrs	55/1114	adjusted/HR	1.26	0.89, 1.77	
					25(OH)D	30—<50	6.5 yrs	146/3430	adjusted/HR	1.19	0.92, 1.55	
					25(OH)D	>=50	6.5 yrs	112/3165	adjusted/HR	1	reference	
				Primary-Fatal Stroke	25(OH)D	per 25	6.5 yrs	313/7709	adjusted/HR	0.91	0.81, 1.02	
					25(OH)D	< 30	6.5 yrs	9/1114	adjusted/HR	1.86	0.74, 4.66	
					25(OH)D	30—<50	6.5 yrs	20/3430	adjusted/HR	1.44	0.68, 3.03	
					25(OH)D	>=50	6.5 yrs	12/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	41/7709	adjusted/HR	0.86	0.61, 1.23	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Perna et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pfeifer et al., 2009	RCT/CCT	51–70 years; healthy; 70 years of age and older; serum vitamin D<78nmol/L	vitamin D and vitamin D metabolites; Osteoporosis; Prior fragility fracture; Pregnant; Severe cardiovascular disease; chronic renal failure, history of drug, alcohol, tobacco, caffeine abuse; hypercalcemia; primary hyperparathyroidism; diabetes mellitus		Manufacturer	Germany (specify city, if given);Bad Pyrmont; Graz, Austria	242/470/74	77 (4)/NR			Serum vitamin D level:55±18 nmol/L Calcium intake: 608±38 mg/d

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pfeifer et al., 2009	RCT/CCT	age height weight gender serum 25(OH)D nutritional calcium intake intact PTH levels	NR	Primary-Falls (>=1)	Vit D3; Ca	1000 mg & 800 IU daily	12 mo	NR/122	Crude/RR	0.73	0.54, 0.96	<0.01
					Ca	1000 mg daily	12 mo	NR/120	Crude/RR	1	Reference	

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Pfeifer et al., 2009	RCT/CCT	age height weight gender serum 25(OH)D nutritional calcium intake intact PTH levels	NR	Secondary-Quadriceps Strength Left Leg	Ca & Vit D3 1000 mg & 800 IU daily		114	211.00 (SD=83)	final= 236 (SD=75)	+12 (-8.6, 32.6)	0.25
					Ca 1000 mg daily		114	217.00 (SD=90)	final= 224 (SD=83)		.
				Secondary-Body Sway Total Length	Ca & Vit D3 1000 mg & 800 IU daily		114	86.00 (SD=32)	final= 81 (SD=32)	-5 (-13, 3)	0.22
					Ca 1000 mg daily		114	90.00 (SD=42)	final= 86 (SD=30)		.
				Secondary-Timed Up And Go (Tug)	Ca & Vit D3 1000 mg & 800 IU daily		114	9.00 (SD=5.9)	final= 7.5 (SD=3.4)	-0.8 (-1.9, 0.3)	0.16
					Ca 1000 mg daily		114	8.50 (SD=3.9)	final= 8.3 (SD=5.1)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Pfeifer et al., 2009	RCT/CCT	ND	ND	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pike et al., 2012	Prospective Cohort	women 20–34 years; children born to these women from 1998 to 2002	infants born at <35 weeks gestation		Private Foundation	UK	860/836/48.26 (children)	30.37 (3.81)/NR		Other; mother/child pairs: slightly more than 20% of mothers had history of asthma and nearly half had atopy	Maternal late serum vitamin D: median 59.00 nmol/L (IQR:40.52–84.89)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pike et al., 2012	Prospective Cohort	NR	NR	Primary-Current Doctor-Diagnosed Asthma	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	87/836	adjusted/RR	0.98	0.92, 1.04	0.56
				Primary-Current Wheeze In Last 12 Months	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	117/833	adjusted/RR	0.99	0.94, 1.05	0.76
				Primary-Any Wheeze At Or Before 6 Years	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	504/823	adjusted/RR	1	0.98, 1.02	0.95
				Primary-Transient Wheeze	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	367/707	adjusted/RR	1	0.98, 1.02	0.89
				Primary-Persistent Late Wheeze	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	137/475	adjusted/RR	0.98	0.94, 1.03	0.49
				Primary-Persistent Late Wheeze With Atopy	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	46/251	adjusted/RR	0.91	0.84, 0.99	0.04
				Primary-Persistent Late Wheeze Without Atopy	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	48/253	adjusted/RR	1.01	0.94, 1.09	0.73

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Pike et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	N	NA	Y	Y	N	B	>20% lost to follow-up but had partial data. Not sure whether sufficient	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pilz et al., 2009	Prospective Cohort	19–50 years; 51–70 years; 50–75 years of age	Not specified	Hoorn Study	Private Foundation	Hoorn, Netherlands	614/614/50	69.2 (3rd quartile) (6.5)/NR	Non-Hispanic White=100	Other; more than 20% Type 2 Diabetes or impaired glucose tolerance	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pilz et al., 2009	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Waist-To-Hip Ratio, Percent Body Fat; Medical Conditions- Hypertension; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - HDL Cholesterol, Glomerular Filtration Rate	Primary-All-Cause Mortality	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	6.2 yrs	21/152	adjusted/HR	1.97	1.08, 3.58	0.027
					25(OH)D	2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	6.2 yrs	30/462	adjusted/HR	1	Reference	
				Primary-Cardiovascular Mortality	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	6.2 yrs	12/152	adjusted/HR	5.38	2.02, 14.34	0.001
					25(OH)D	2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	6.2 yrs	8/462	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Pilz et al., 2009	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	Alicia didn't actually record selections. Large loss to followup.

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Powe et al., 2010	Nested Case Control	Pregnant or lactating women; nulliparous; Delivering singleton live births after 20 weeks gestation	Hypertension; history of diabetes; thyroid, liver, chronic renal disease; pre-existing chronic hypertension	MGH Obstetric Maternal Study	Private Foundation	USA; Boston	170/NR/100	30.4 (6.0)/NR	Non-Hispanic White=664	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Powe et al., 2010	Nested Case Control	gestational age at blood draw	Demographics (Age, Sex, Race/Ethnicity)- BMI, Race; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Blood Collection	Primary-Severe Preeclampsia	25(OH)D	Quartile 1 (ND)	NR	39 (overall)/ NR	adjusted/OR	1.5	0.57, 3.96	
					25(OH)D	Quartile 2 (ND)	NR		adjusted/OR	1.04	0.39, 2.76	
					25(OH)D	Quartile 3 (ND)	NR		adjusted/OR	0.67	0.23, 1.91	
					25(OH)D	Quartile 4 (ND)	NR		adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Powe et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Prentice et al., 2013	RCT/CCT	Postmenopausal women; age 50–79; intending to reside in area for ≥3 years	intention to continue taking = 600 IU per day; current use of calcitriol; current use of daily corticosteroids; Any invasive cancer in prior 10 years, breast cancer, no mammogram within 2 years prior to enrollment; self-reported urinary tract stones	WHI	Private Foundation	USA; multiple sites	36,282/30604/ 100	50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%/50–79	Non-Hispanic White=831; Hispanic=42; Non-Hispanic Black=91; Asian=20; Race_other1=04; Race_other2=12	Post menopausal	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Prentice et al., 2013	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Usual Intake Of Vitamin D And Calcium; Demographics (Age, Sex, Race/Ethnicity)- Baseline Age, Non-White Ethnicity; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Current Or Past Cigarette Smoking	Primary-Total Fracture	D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	872/7718	adjusted/HR	0.97	0.88, 1.07	NR
				Primary-Hip Fracture	D3; calcium carbonate	placebo	7.2 yrs	870/7584	adjusted/HR	1	reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	68/7718	adjusted/HR	0.86	0.62, 1.20	NR
				Primary-Total Invasive Cancer	D3; calcium carbonate	placebo	7.2 yrs	80/7584	adjusted/HR	1	reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	553/7718	adjusted/HR	0.88	0.78, 0.98	NR
				Primary-Death	D3; calcium carbonate	placebo	7.2 yrs	617/7584	adjusted/HR	1	reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	331/7718	adjusted/HR	0.95	0.81, 1.11	NR
				Primary-MI	25(OH)D3; calcium carbonate	placebo	7.2 yrs	338/7584	adjusted/HR	1	reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	193/7718	Adjusted/HR	1.18	0.88, 1.59	0.17
				Primary-Coronary Heart Disease	25(OH)D3; calcium carbonate	placebo	7 yrs	167/7584	Adjusted/HR	1	Reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	229/7718	Adjusted/HR	1.08	0.82, 1.42	0.4
				Primary-Total Heart Disease	25(OH)D3; calcium carbonate	placebo	7 yrs	211/7584	Adjusted/HR	1	Reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	621/7718	Adjusted/HR	1	0.86, 1.18	0.56
				Primary-Stroke	25(OH)D3; calcium carbonate	placebo	7 yrs	642/7584	Adjusted/HR	1	Reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	184/7718	Adjusted/HR	1.18	0.86, 1.62	0.96
				Primary-Total Cardiovascular Disease	25(OH)D3; calcium carbonate	placebo	7 yrs	162/7584	Adjusted/HR	1	Reference	
						1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	848/7718	Adjusted/HR	1.04	0.90, 1.19	0.77
						placebo	7 yrs	813/7584	Adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Prentice et al., 2013	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Prince et al., 2008	RCT/CCT	51–70 years; older women; history of falling in the prior 12 months; serum vitamin D<24.0ng/ml	current vitamin D consumption; Other systemic bone disease (e.g., Paget's); current consumption of bone or mineral active agents other than calcium; bone mineral density z-score at the hip of <-2.0; fracture in the past 6 months; marked neurological conditions; medical conditions that influence bone mineral metabolism		Manufacturer	Australia;Perth	302/302/100	77.4 (5.0)/70–90		Vitamin d deficient/depleted	Serum vitamin D: 17.7±5.1 ng/mL

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Prince et al., 2008	RCT/CCT	NR	NR	Primary-Falls (>=1)	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	80/151	Adjusted/OR	0.61	0.37, 0.99	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	95/151	Adjusted/OR	1	Reference	
				Primary-1 Fall	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	32/151	Crude/OR	0.5	0.28, 0.88	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	51/151	Crude/OR	1	Reference	
				Primary-Falls (=2)	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	NR/151	Crude/OR	0.86	0.50, 1.49	> 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	NR/151	Crude/OR	1	Reference	
				Primary-First Fall In Winter/Spring	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	38/151	Crude/OR	0.55	0.32, 0.96	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	54/151	Crude/OR	1	Reference	
				Primary-First Fall In Summer/Autumn	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	42/151	Crude/OR	0.81	0.46, 1.42	> 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	41/151	Crude/OR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Prince et al., 2008	RCT/CCT	Y	ND	Y	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Racovan et al., 2012	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–79 years at baseline; no evidence of a medical condition associated with a predicted survival of less than 3 years	calcitriol use; corticosteroid use; hypercalcemia, renal calculi	WHI	Government	USA; multiple	32,435/32521/ 100	62.34 (6.91)/NR	Non-Hispanic White=8415; Hispanic=382; Non-Hispanic Black=846; Asian=203; Race_other1=120; Race_other2=035	Post menopausal	categories: <200, 200–<400, 400–<600, >=600 IU/day

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Racovan et al., 2012	RCT/CCT	Age, race/ethnicity, BMI, solar irradiance, total vitamin D intake, multivitamin use, education, HT, smoking history, alcohol consumption, or breastfeeding history.	NR	Primary-Rheumatoid Arthritis	Vit D; Calcium 1000ng	400IU-NR	5.1 years	45/16283	Adjusted/HR	1.15	0.75, 1.75	0.53
					Vit D; Calcium 1000ng	Placebo-NR	5.1 years	41/16238	Adjusted/HR	1	reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Racovan et al., 2012	RCT/CCT	Y	Y	NA	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Rejnmark et al., 2009	Nested Case Control	Referred for mammogram; No previous breast cancer	Not specified		Private Foundation	Denmark	562/NR/100	58/29–87			

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Rejnmark et al., 2009	Nested Case Control	age, menopausal status, season of blood draw, body weight, calcium intake, smoking habits, fresh fruit consumption, alcohol intake	NR	Primary-Breast Cancer	25(OH)D	<60nmo/L	NR	NR/NR	adjusted/RR	1	reference	
					25(OH)D	60–84nmol/L	NR	NR/NR	adjusted/RR	0.94	0.59, 1.47	
					25(OH)D	>84nmol/L	NR	NR/NR	adjusted/RR	0.52	0.32, 0.85	<0.05
					25(OH)D	<60nmo/L-Premenopausal women	NR	NR/NR	adjusted/RR	1	reference	
					25(OH)D	60–84nmol/L- Premenopausal women	NR	NR/NR	adjusted/RR	0.59	0.26, 1.33	
					25(OH)D	>84nmol/L- Premenopausal women	NR	NR/NR	adjusted/RR	0.38	0.15, 0.97	<0.05
					25(OH)D	<60nmo/L- Postmenopausal women	NR	NR/NR	adjusted/RR	1	reference	
					25(OH)D	60–84nmol/L- Postmenopausal women	NR	NR/NR	adjusted/RR	1.2	0.67, 2.16	
					25(OH)D	>84nmol/L- Postmenopausal women	NR	NR/NR	adjusted/RR	0.71	0.38, 1.30	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Rejnmark et al., 2009	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Roth et al., 2013	RCT/CCT	9–18 years; 19–50 years; Pregnant or lactating women; age 18–<35 years; gestational age of 26–<30 weeks; current residence in Dhaka at a fixed address; planned to deliver at the Shimantik maternity center	use of any dietary supplement containing more than 400 IU/ day (10 mcg/day) of vitamin D within the month prior to enrolment, or refusal to stop taking supplemental vitamin D at any dose after enrollment; current use of anticonvulsant or anti-mycobacterial (tuberculosis) medications; severe anemia (hemoglobin < 70 g/L); systolic blood pressure =140 mm Hg or diastolic blood pressure =90 mm Hg; positive urine dipstick for proteinuria or glycosuria; complicated medical or obstetric history; reported prior history of delivery of an infant with a major congenital anomaly, birth asphyxia, or perinatal death	Antenatal Vitamin D in Dhaka (AViDD) trial	Private Foundation	Dhaka, Bangladesh	160/147/100	22.4 (3.5)/NR			Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Roth et al., 2013	RCT/CCT	NR	NR	Secondary-Birth Weight	35000 IU Vit D3 3rd trimester		73	NR (NR)	Final=2802 (2675, 2929)	+14 (-138, 166)	0.86
					Placebo		74	NR (NR)	Final=2788 (2700, 2876)	.	.
				Secondary-Length At Birth	35000 IU Vit D3 3rd trimester		73	NR (NR)	Final=48.2 (47.6, 48.8)	+0.2 (-0.5, 0.9)	0.55
					Placebo		74	NR (NR)	Final=48 (47.5, 48.5)	.	.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization (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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Roth et al., 2013	RCT/CCT	Y	Y	N	Y	Y	Y	ND	N	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Rouzi et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Postmenopausal women; Healthy; age=50 years; independent mobility; unrestricted diet; normal liver, renal function	Osteoporosis; Prior cancer; Current cancer; t-score<-2.5		Government	Jeddah, Saudi Arabia	707/707/100	61.3 (7.2)/NR		Post menopausal	Serum 25(OH)D: 34.27±22.80 nmol/L	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Rouzi et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Smoking, Other Lifestyle Factors- Smoking, Coffee/Tea Consumption; Other - Previous Fractures, Hormone Levels, Bone Turnover Markers	Primary-Fragility Fractures	25(OH)D	<17.90 nmol/L	5.2 yrs	138/707	adjusted/OR	1.25	0.91, 1.70	
					25(OH)D	>45.1 nmol/L	5.2 yrs		adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Rouzi et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	Y	Y	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sabetta et al., 2010	Prospective Cohort	Healthy	Current cardiovascular disease; Type 2 DM; Pregnant; chronic pulmonary, renal hepatic, hematologic, neurologic, neuromuscular, or metabolic disorder; immunosuppression; high-dose aspirin therapy		a private family	USA; Greenwich, CT	198/198/57	NR/20–88	Race_other1= 78; Race_other2= 16; Race_other3= 6		Serum vitamin D: 28.4±0.8 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sabetta et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Use Of Vitamins Other Than D, Herbs And Other Supplements; Demographics (Age, Sex, Race/Ethnicity)- Sex, Age; Anthropometrics- Skin Pigmentation; Other - Receipt Of Seasonal and/or H1n1 Influenza Vaccine	Primary-Acute Viral Respiratory Tract Infections	25(OH)D	>=38ng/ml	4 months	3/18	Crude/OR	0.24	0.07, 0.87	
					25(OH)D	<38ng/ml	4 months	81/180	Crude/OR	1	reference	0.015

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sabetta et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	no inclusion criteria

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salehpour et al., 2012	RCT/CCT	9–18 years; 19–50 years; Healthy; women; 18–50 years of age; BMI=25kg/m2; free of known osteoporosis, gastrointestinal disease, diabetes mellitus, CVD, renal disease, hypertension	Pregnant; any; On a weight loss program; taking weight loss drugs; weight change of >3kg during the prior 3 months; lactating; smoking; drinking alcohol; taking nutrition supplements, cholesterol or TAG-lowering agents as well as anti-hypertensive agents		university	Tehran, Iran	85/85/100	38 (8.1)/NR		Overweight/obese	S-25(OH)D Vit D group - 36.8 +/- 30 nmol/l Placebo group - 46.9 +/- 32 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Salehpour et al., 2012	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Dietary Intake; Anthropometrics- Fat Mass, Waist Circumference; Smoking, Other Lifestyle Factors- Physical Activity (Not Smoking)	Secondary-DBP	D3 Vit D 25 µg/day		42	67.9 (sd=10.1)	final=70.2 (sd=8.8)	-1.9 (-6.1, 2.3)	.
					D3 placebo		43	71.9 (sd=9.1)	final=72.1 (sd=10.6)		.
				Secondary-SBP	D3 Vit D 25 µg/day		42	110.5 (sd=17.5)	final=111 (sd=11.3)	-3.4 (-8.7, 1.9)	.
					D3 placebo		43	116.7 (sd=11.4)	final=114.4 (sd=13)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Salehpour et al., 2012	RCT/CCT	Y	ND	N	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salovaara et al., 2010	RCT/CCT	51–70 years; women; Birth between 1932 and 1941; Age 65 and over at current followup; Residence in Northern Savonia		OSTPRE Study	Hospital	Finland	3195/3195/100	67.3 (1.8)/NR		Not Reported	Serum vitamin D: 49.1±17.7 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salovaara et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Use Of Alcohol; Other - Parental Hip Fracture, Glucocorticoid Use, Diagnosed Rheumatoid Arthritis, Secondary Osteoporosis	Primary-Any Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	78/1586	adjusted/HR	0.83	0.61, 1.12	
						control (no intervention or placebo)	3.01 yrs	94/1609	adjusted/HR	1	Reference	
				Primary-Any Nonvertebral Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	71/1586	adjusted/HR	0.87	0.63, 1.19	
						control (no intervention or placebo)	3.01 yrs	82/1609	adjusted/HR	1	Reference	
				Primary-Any Osteoporotic Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	42/1586	adjusted/HR	0.81	0.54, 1.22	
						control (no intervention or placebo)	3.01 yrs	52/1609	adjusted/HR	1	Reference	
				Primary-Distal Forearm Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	23/1586	adjusted/HR	0.7	0.41, 1.20	
						control (no intervention or placebo)	3.01 yrs	32/1609	adjusted/HR	1	Reference	
				Primary-Proximal Humerus Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	6/1586	adjusted/HR	1.01	0.32, 3.14	
						control (no intervention or placebo)	3.01 yrs	6/1609	adjusted/HR	1	Reference	
				Primary-Hip Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	4/1586	adjusted/HR	2.23	0.41, 12.29	
						control (no intervention or placebo)	3.01 yrs	2/1609	adjusted/HR	1	Reference	
				Primary-Vertebral Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	9/1586	adjusted/HR	0.67	0.29, 1.58	
						control (no intervention or placebo)	3.01 yrs	13/1609	adjusted/HR	1	Reference	
				Primary-Upper Extremity Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	41/1586	adjusted/HR	0.75	0.49, 1.16	
						control (no intervention or placebo)	3.01 yrs	50/1609	adjusted/HR	1	Reference	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
				Primary-Lower Extremity Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	22/1586	adjusted/HR	1.02	0.58, 1.80	
						control (no intervention or placebo)	3.01 yrs	20/1609	adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Salovaara et al., 2010	RCT/CCT	Y	Y	ND	Y	N	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Salzer et al., 2012	Nested Case Control	19–50 years; 51–70 years; Individuals 30, 40, 50, and 60 years of age; women 50–69 years of age; residence in Vasterbotten Sweden; no symptoms of MS prior to blood sampling	Not specified	Risk of Multiple Sclerosis	Manufacturer	Sweden	576/576/92.2	26/16–60	Race_other1= 99; Race_other2= 1	Not Reported	Serum vitamin D: 40nmol/L (range 0–122)	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salzer et al., 2012	Nested Case Control	Sex, biobank, sampling date, age	NR	Primary-Multiple Sclerosis	25(OH)D	>=75nmol/l	NR	192/576	Adjusted/OR	0.39	0.16, 0.98	NR
					25(OH)D	<75nmol/l	NR		Adjusted/OR	1	reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Salzer et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	Y	Y	N	N	A	Sampling = Consecutive	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salzer et al., 2012	Nested Case Control	Pregnant or lactating women	Not specified	Gestational Risk factors of Multiple Sclerosis (GRoMS)	Manufacturer	Sweden	222/222/100	27/19–40			Serum vitamin D: 40nmol/L (0–335)_

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salzer et al., 2012	Nested Case Control	sex, biobank, sampling date, age	NR	Primary-Multiple Sclerosis	25(0H)D	>=75nmol/l	NR	37/222	Adjusted/OR	1.8	0.53, 5.8	NR
					25(0H)D	<75nmol/l	NR		Adjusted/OR	1	reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Salzer et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	Y	Y	N	N	A	Sampling = Consecutive	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Schierbeck et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Postmenopausal women; Healthy; women; Age 45–58; Recently postmenopausal with last menstrual bleeding 3–24 months before enrollment or perimenopausal with elevated FSH; Caucasian	Osteoporosis; Other systemic bone disease (e.g., Paget's); Prior fragility fracture; Prior cancer; Current cancer; Uncontrolled chronic disease, thromboembolic disease; Current or past treatment with glucocorticoids, alcohol or drug addiction; Current or previous post-menopausal hormone therapy in past 3 months	Danish Osteoporosis Prevention Study	University	Denmark	2,013/2013/100	50.0 (2.8)/NR	Non-Hispanic White=100	Post menopausal	Serum 25(OH)D: Low vitamin D group: 35±10 High vitamin D group: 80±26

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Schierbeck et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- Waist-Hip Ratio; Smoking, Other Lifestyle Factors- Smoking; Other - Family History Of MI, Use Of Menopausal Hormone Therapy Was Not Controlled For But Did Not Differ Between High And Low Vitamin D Groups	Primary-Heart Failure	25(OH)D	<50 nmol/l	16 yrs	10/788	Adjusted/HR	1.88	0.71, 5.01	0.206
					25(OH)D	>=50 nmol/l	16 yrs	8/1225	Adjusted/HR	1	Reference	
				Primary-Myocardial Infarction	25(OH)D	<50 nmol/l	16 yrs	13/788	Adjusted/HR	0.83	0.41, 1.67	0.597
					25(OH)D	>=50 nmol/l	16 yrs	22/1225	Adjusted/HR	1	Reference	
				Primary-Stroke	25(OH)D	<50 nmol/l	16 yrs	47/788	Adjusted/HR	1.68	1.10, 2.56	0.017
					25(OH)D	>=50 nmol/l	16 yrs	42/1225	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Schierbeck et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Scholl et al., 2013	Prospective Cohort	Pregnant or lactating women	Current cancer; Hypertension; Type 2 DM; Autoimmune disease; Type 1 diabetes; seizure disorders; drug or alcohol abuse; other serious non-obstetric conditions	Camden Study	Government	USA; Camden NJ	1,141/1141/100	22.8 (5.4)/NR	Non-Hispanic White=140; Hispanic=513; Non-Hispanic Black=347	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Scholl et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors- Total Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking; Other - Gestational Stage At Entry	Primary- Preeclampsia	25(OH)D	<30	20 weeks gestation	12/121	adjusted/OR	2.13	1.07, 4.26	0.027
					25(OH)D	30–40	20 weeks gestation	12/116	adjusted/OR	2.09	1.04, 4.22	
					25(OH)D	40–50	20 weeks gestation	7/154	adjusted/OR	0.94	0.41, 2.17	
					25(OH)D	>=50	20 weeks gestation	38/750	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Scholl et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Schottker et al., 2013	Prospective Cohort	51–70 years; age 50–74 years	Not specified	ESTHER	Government	Germany (specify city, if given)	9578/9578/56.2	62 (6.5)/NR		Not Reported	25(OH)D: 51.1 +/- 24.6 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Schottker et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Regular Intake Of Multivitamin Supplements, Fish Consumption; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Medical Conditions- Chronic Kidney Disease, Diabetes, Hypertension, Cardiovascular Disease, Cancer; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking; Other - Serum C-Reactive Protein Concentrations, Total Cholesterol	Primary-All-Cause Mortality	25(OH)D	<30	9.5 yrs	238/1444	adjusted/HR	1.68	1.41, 2.01	
					25(OH)D	30–50	9.5 yrs	448/4199	adjusted/HR	1.17	1.01, 1.35	
					25(OH)D	>50	9.5 yrs	397/3935	adjusted/HR	1	reference	
					25(OH)D	<30->=65 years of age	9.5 yrs	142/609	adjusted/HR	1.41	1.13, 1.77	
					25(OH)D	30–50->=65 years of age	9.5 yrs	269/1706	adjusted/HR	1.09	0.90,1.31	
					25(OH)D	>50->=65 years of age	9.5 yrs	236/1394	adjusted/HR	1	reference	
					25(OH)D	<30–<65 years of age	9.5 yrs	238/835	adjusted/HR	2.08	1.58, 2.76	
					25(OH)D	30–50–<65 years of age	9.5 yrs	448/2493	adjusted/HR	1.3	1.04, 1.63	
				Secondary-Cvd Mortality	25(OH)D	>50–<65 years of age	9.5 yrs	397/2541	adjusted/HR	1	reference	
					25(OH)D	<30	9.5 yrs	71/1439	adjusted/HR	1.29	0.94, 1.76	
					25(OH)D	30–50	9.5 yrs	137/4188	adjusted/HR	0.94	0.73, 1.21	
					25(OH)D	>50	9.5 yrs	142/3927	adjusted/HR	1	reference	
				Secondary-Cancer Mortality	25(OH)D	<30	9.5 yrs	90/1439	adjusted/HR	1.42	1.08, 1.87	
					25(OH)D	30–50	9.5 yrs	172/4188	adjusted/HR	1.04	0.83, 1.29	
					25(OH)D	>50	9.5 yrs	171/3927	adjusted/HR	1	reference	
				Secondary-Respiratory Disease Mortality	25(OH)D	<30	9.5 yrs	13/1439	adjusted/HR		NR	
					25(OH)D	30–50	9.5 yrs	26/4188	adjusted/HR		NR	
					25(OH)D	>50	9.5 yrs	16/3927	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Schottker et al., 2013	N	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Science et al., 2013	Prospective Cohort	3–8 years; 9–18 years; age 3–15 years	underlying chronic medical conditions		Government	Canada	947/743/52.5	9.3 (3.4)/NR		Not Reported	serum 25(OH)D: median (IQR) 62.0 (51.0–74.0) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Science et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex	Primary-Respiratory Tract Infections	25(OH)D	per 1-unit change in log levels	156 days	229/743	adjusted/HR	0.52	0.35, 0.79	0.002
					25(OH)D	<25	156 days	NR/4	unadjusted/HR	0.72	0.13, 3.94	0.7
					25(OH)D	>=25	156 days	NR/739	unadjusted/HR	1	Reference	
					25(OH)D	<50	156 days	NR/152	unadjusted/HR	1.54	1.07, 2.21	0.021
					25(OH)D	>=50	156 days	NR/591	unadjusted/HR	1	Reference	
					25(OH)D	<75	156 days	NR/565	unadjusted/HR	1.35	1.01, 1.82	0.043
					25(OH)D	>=75	156 days	NR/178	unadjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Science et al., 2013	Y	N	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Scott et al., 2010	Prospective Cohort	19–50 years; 51–70 years; on electoral rolls in southern Tasmania; community dwelling	institutionalized; contraindications to MRI	Tasmanian Older Adult Cohort Study (TASOAC)	University	Australia; Tasmania	686/686/49	62 (7)/50–79	Non-Hispanic White=98	Not Reported	Serum 25OH(D) Low vitamin D: 37.1±8.4 High vitamin D: 67.8±13.4

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Scott et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Use Of Vitamin D Supplements; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Sun Exposure- Self-Reported Sun Exposure And Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity	Secondary-Appendicular Lean Mass	25(OH)D > 50nmol/l		389	62.20 (SD=9.6)	NR (NR)	+0.01 (-0.52, 0.54)	0.963
					25(OH)D = 50nmol/l		297	59.30 (SD=9.9)	NR (NR)		.
				Secondary-Leg Strength	25(OH)D > 50nmol/l		389	100.80 (SD=50.1)	NR (NR)	+5.74 (0.65, 10.82)	0.027
					25(OH)D = 50nmol/l		297	91.50 (SD=47.8)	NR (NR)		.
				Secondary-Leg Muscle Quality	25(OH)D > 50nmol/l		389	5.90 (SD=2.3)	NR (NR)	+0.49 (0.17, 0.82)	0.003
					25(OH)D = 50nmol/l		297	5.50 (SD=2.3)	NR (NR)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Scott et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	random except stratified by sex loss to follow-up = 20%

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Semba et al., 2010	Prospective Cohort	51–70 years; adults=65 years of age; community dwelling	Not specified	InCHIANTI		Italy	1,006/NR/32.7	78.0/72.0–85.0			

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Semba et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Blood Lipids, Renal Insufficiency, Mini Mental Status Exam Score	Primary-All-Cause Mortality	25(OH)D	Q1:<26.2 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.11	1.22, 3.64	NR
					25(OH)D	Q2:26.2–40 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.41	0.83, 2.40	
					25(OH)D	Q3: 40–63.9 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.12	1.09, 1.15	
					25(OH)D	Q4: >63.6 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1	reference	
				Primary-Cardiovascular Disease Mortality	25(OH)D	Q1:<26.2 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.64	1.68, 2.19	NR
					25(OH)D	Q2:26.2–40 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.68	0.76, 3.72	
					25(OH)D	Q3: 40–63.9 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.19	1.05, 4.60	
					25(OH)D	Q4: >63.6 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Semba et al., 2010	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B	design b- unclear	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sempos et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age >=20 years	Pregnant; missing information on vital status; missing data for serum total 25(OH)D, serum creatinine, SBP; no follow-up time from data of examination	NHANES III	Government	USA	15099/15099/51	45 (SE=0.47)/NR	Non-Hispanic White=77; Hispanic=5; Non-Hispanic Black=10; Race_other1=8	Not Reported	Serum 25(OH)D 64 nmol/liter (SE 0.73)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sempos et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Sun Exposure-Season	Primary-Death From All-Cause	25(OH)D	<20	15 yrs	79/251	adjusted/RR	1.6	1.2, 2.2	
					25(OH)D	20–29	15 yrs	297/1270	adjusted/RR	1.5	1.2, 1.8	
					25(OH)D	30–39	15 yrs	592/2340	adjusted/RR	1.3	1.1, 1.5	
					25(OH)D	40–49	15 yrs	694/2790	adjusted/RR	1.1	0.96, 1.3	
					25(OH)D	50–59	15 yrs	668/2526	adjusted/RR	1.2	1.01, 1.30	
					25(OH)D	60–74	15 yrs	775/3046	adjusted/RR	1.1	0.99, 1.30	
					25(OH)D	75–99	15 yrs	533/2156	adjusted/RR	1	Reference	
					25(OH)D	100–119	15 yrs	110/518	adjusted/RR	1.1	0.9, 1.4	
					25(OH)D	>=120	15 yrs	36/202	adjusted/RR	1.4	0.9, 2.2	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sempos et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	ref 9: http://www.cdc.gov/nchs/data/series/sr_01/sr01_032.pdf

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shand et al., 2010	Prospective Cohort	9–18 years; 19–50 years; Pregnant or lactating women; =18 years; 10–20 weeks gestation; increased risk for pre-eclampsia	Not specified	EMMA	none	Canada; Vancouver CA	227/NR/100	NR/NR	Non-Hispanic White=611; Race_other1=204; Race_other2=136; Race_other3=5		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Shand et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking Status	Primary- Preeclampsia	25(OH)D	<37.5	10–20 weeks gestation	10/NR	adjusted/OR	0.91	0.31, 2.62	
					25(OH)D	>=37.5	10–20 weeks gestation	18/NR	adjusted/OR	1	Reference	
					25(OH)D	<50	10–20 weeks gestation	17/NR	adjusted/OR	1.39	0.54, 3.53	
					25(OH)D	>=50	10–20 weeks gestation	11/NR	adjusted/OR	1	Reference	
					25(OH)D	<75	10–20 weeks gestation	21/NR	adjusted/OR	0.57	0.19, 1.66	
					25(OH)D	>=75	10–20 weeks gestation	6/NR	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Shand et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shin et al., 2013	Prospective Cohort	Pregnant or lactating women	diabetes; preeclampsia; anemia; severe infections during pregnancy	COhort for Childhood Origin of Asthma and allergic diseases (COCOAA)	Government	Korea	1545/525/mothers: 100, newborns: 46.9	maternal age: 32.2 (maternal age: 3.4)/newborns: 0–6 months		Not Reported	mean cord blood plasma 25(OH)D 32.0 nmol/L (IQR, 21.4 to 53.2)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Shin et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use During Pregnancy; Sun Exposure- Season Of Birth; Smoking, Other Lifestyle Factors- Exposure To Passive Smoking During Pregnancy	Primary-Respiratory Tract Infections	25(OH)D	<25.0	6 months	74/180	adjusted/OR	3.41	1.57, 7.42	0.0008
					25(OH)D	25.0–74.9	6 months	89/292	adjusted/OR	2.14	1.00, 4.58	
					25(OH)D	>=75.0	6 months	9/53	adjusted/OR	1	Reference	
				Primary-Acute Nasopharyngitis	25(OH)D	<25.0	6 months	67/180	adjusted/OR	4.64	1.88, 11.44	0.0002
					25(OH)D	25.0–74.9	6 months	75/292	adjusted/OR	2.71	1.11, 6.59	
					25(OH)D	>=75.0	6 months	6/53	adjusted/OR	1	Reference	
				Primary-Otitis Media	25(OH)D	<25.0	6 months	10/180	adjusted/OR	3.06	0.38, 24.46	0.3625
					25(OH)D	25.0–74.9	6 months	18/292	adjusted/OR	3.42	0.45, 26.15	
					25(OH)D	>=75.0	6 months	1/53	adjusted/OR	1	Reference	
				Primary-Bronchiolitis	25(OH)D	<25.0	6 months	9/180	adjusted/OR	2.74	0.34, 22.11	0.4819
					25(OH)D	25.0–74.9	6 months	19/292	adjusted/OR	3.62	0.47, 27.63	
					25(OH)D	>=75.0	6 months	1/53	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Shin et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shui et al., 2012	Nested Case Control	US male health professionals aged 40–75 in 1986; provided chilled blood sample between 1993 and 1995; For controls, PSA test within 2.5 years of date of diagnosis of matched case	cases with T1a tumors	Health Professionals' Follow-up Study	Private Foundation	USA	2,591/2584/0	64.4 (7.8)/NR	Non-Hispanic White=95; Not reported=5	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Shui et al., 2012	Nested Case Control	age, PSA test before blood collection, time (of day) of blood collection, season of blood collection, year	Other Nutrients Or Dietary Factors- Energy Adjusted Lycopene And Calcium Intakes, Total Energy Intake, Red Meat Servings Per Week, Fish Servings Per Week; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI, Height; Medical Conditions- Type 2 Diabetes Status; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Coffee Intake, Vigorous Physical Activity; Other - Follow-Up Time, Family History Of Prostate Cancer, Vasectomy Status	Primary-Lethal Prostate Cancer	25(OH)D	Quartile 1	5.2 years	41/366	adjusted/OR	1	reference	
					25(OH)D	Quartile 2	5.2 years	33/369	adjusted/OR	0.78	0.47, 1.30	
					25(OH)D	Quartile 3	5.2 years	21/335	adjusted/OR	0.5	0.28, 0.88	
					25(OH)D	Quartile 4	5.2 years	19/348	adjusted/OR	0.44	0.24, 0.79	0.002
				Primary-Overall Prostate Cancer	25(OH)D	Quartile 1	5.2 years	310/635	adjusted/OR	1	reference	
					25(OH)D	Quartile 2	5.2 years	298/634	adjusted/OR	0.93	0.74, 1.17	
					25(OH)D	Quartile 3	5.2 years	319/653	adjusted/OR	0.99	0.79,1.24	
					25(OH)D	Quartile 4	5.2 years	333/662	adjusted/OR	1.07	0.86, 1.34	0.450
				Primary-Advance Stage At Diagnosis	25(OH)D	Quartile 1	5.2 years	51/376	adjusted/OR	1	reference	
					25(OH)D	Quartile 2	5.2 years	43/379	adjusted/OR	0.96	0.61, 52	
					25(OH)D	Quartile 3	5.2 years	32/366	adjusted/OR	0.63	0.39, 1.03	
					25(OH)D	Quartile 4	5.2 years	40/662	adjusted/OR	0.85	0.53,1.35	0.220
				Primary-High Grade Prostate Cancer	25(OH)D	Quartile 1	5.2 years	69/394	adjusted/OR	1	reference	
					25(OH)D	Quartile 2	5.2 years	55/391	adjusted/OR	0.81	0.54, 1.21	
					25(OH)D	Quartile 3	5.2 years	51/385	adjusted/OR	0.75	0.50, 1.13	
					25(OH)D	Quartile 4	5.2 years	64/393	adjusted/OR	0.99	0.67, 1.46	0.870

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Shui et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	NA	Y	N	N	A	very minimal eligibility criteria	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Signorello et al., 2013	Prospective Cohort	19–50 years; 51–70 years; 40–79 years of age; English speaking; No cancer treatment within the previous year	Not specified	Southern Community Cohort Study	Government	USA	3,704/3704/NR	NR/NR	Non-Hispanic White=27; Non-Hispanic Black=69; Not reported=4	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Signorello et al., 2013	Prospective Cohort	sex, race, age at enrollment, enrollment site, date of blood collection	Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking Status, Total Physical Activity	Primary-All-Cause Mortality	25(OH)D	Quartile 4: (>21.64 ng/mL)	NR	364/827	adjusted/OR	1	Reference	<0.001
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)	NR	405/868	adjusted/OR	1.17	0.95, 1.45	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)	NR	482/945	adjusted/OR	1.41	1.14, 1.74	
					25(OH)D	Quartile 1: <10.18 ng/mL)	NR	601/1064	adjusted/OR	1.8	1.43, 2.27	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-African Americans	NR	181/400	adjusted/OR	1	Reference	0.003
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-African Americans	NR	266/565	adjusted/OR	1.15	0.87, 1.53	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-African Americans	NR	353/730	adjusted/OR	1.19	0.91, 1.57	
					25(OH)D	Quartile 1: <10.18 ng/mL)-African Americans	NR	475/855	adjusted/OR	1.6	1.20, 2.14	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-non African Americans	NR	179/419	adjusted/OR	1	Reference	<0.001
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-non African Americans	NR	136/296	adjusted/OR	1.09	0.78, 1.52	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-non African Americans	NR	129/214	adjusted/OR	1.99	1.37, 2.90	
					25(OH)D	Quartile 1: <10.18 ng/mL)-non African Americans	NR	122/203	adjusted/OR	2.11	1.39, 3.21	
				Primary-Cancer Death	25(OH)D	Quartile 4: (>21.64 ng/mL)	NR	115/228	adjusted/OR	1	Reference	0.53
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)	NR	102/228	adjusted/OR	0.79	0.52, 1.21	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)	NR	127/255	adjusted/OR	1.03	0.66, 1.59	
					25(OH)D	Quartile 1: <10.18 ng/mL)	NR	133/243	adjusted/OR	1.28	0.78, 2.11	
				Primary-Circulatory Disease Death	25(OH)D	Quartile 4: (>21.64 ng/mL)-African Americans	NR	41/109	adjusted/OR	1	Reference	0.01
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-African Americans	NR	76/162	adjusted/OR	1.67	0.95, 2.93	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-African Americans	NR	116/225	adjusted/OR	1.78	1.05, 3.01	0.01
					25(OH)D	Quartile 1: <10.18 ng/mL)-African Americans	NR	144/258	adjusted/OR	2.53	1.44, 4.46	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-non African Americans	NR	40/107	adjusted/OR	1	Reference	
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-non African Americans	NR	38/84	adjusted/OR	1.09	0.51, 2.30	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-non African Americans	NR	37/56	adjusted/OR	3.66	1.50, 8.95	
					25(OH)D	Quartile 1: <10.18 ng/mL)-non African Americans	NR	39/61	adjusted/OR	3.25	1.33, 7.93	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Signorelli et al., 2013	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Simpson et al., 2011	Prospective Cohort	0–6 months; 7 months–2 years; 3–8 years; birth to 8 years of age at recruitment; born at St. Joseph's Hospital in Denver CO; positive for diabetes-susceptibility alleles in the HLA region	Not specified	Diabetes Autoimmunity Study in the Young (DAISY)	Private Foundation	USA; Denver CO	185/185/51	11.9 (4.4)/NR	Non-Hispanic White=76	Other; at increased risk for Type 1 diabetes	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Simpson et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Ethnicity; Other - HLA Genotype,, Age At First Islet Autoimmunity Positivity	Primary-Islet Autoimmune (IA)	25(OH)D; 9months	Inadequate (<=50nmol/L vs adequate)-Study 1c	NR	30/128	Adjusted/HR	0.72	0.24, 2.17	0.56
				Primary-Type 1 Diabetes In IA Positive	25(OH)D	Inadequate (<=50nmol/L vs adequate)-Study 2b	NR	55/185	Adjusted/HR	0.44	0.14, 1.45	0.18

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Simpson et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Skaaby et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age 30–71 years	Not specified	Monica10 and Inter99	Private Foundation	Denmark	2649 (Monica10), 6497 (Inter99)/8329/49.8 (Monica10), 50.8 (Inter99)	55.4 (Monica10), 46.1 (Inter99)/41.0–72.8 (Monica10), 29.7–61.3 (Inter99)		Not Reported	Median vitamin D 61.0 nmol/l, interquartile range 44.7–80.9 nmol/l (Monica10); median 48.0 nmol/l, interquartile range 32.0–65.0 nmol/l (Inter99).

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Skaaby et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Gender; Medical Conditions- Body Mass Index; Sun Exposure- Season Of Blood Sample; Smoking, Other Lifestyle Factors- Intake Of Fish, Physical Activity, Smoking Habits, Alcohol Consumption; Other - Education	Primary-Ischemic Heart Disease	25(OH)D	per 10nmol/L	10 yrs	478/8131	adjusted/HR	1.01	0.98, 1.05	0.44
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.25
					25(OH)D	Q2	10 yrs		adjusted/HR	1.17	0.91, 1.51	
					25(OH)D	Q3	10 yrs		adjusted/HR	1	0.76, 1.31	
					25(OH)D	Q4	10 yrs		adjusted/HR	1.24	0.95, 1.62	
				Primary-Stroke	25(OH)D	per 10nmol/L	10 yrs	316/8131	adjusted/HR	1	0.96, 1.05	0.92
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.78
					25(OH)D	Q2	10 yrs		adjusted/HR	1.08	0.79, 1.49	
					25(OH)D	Q3	10 yrs		adjusted/HR	1.18	0.86, 1.63	
					25(OH)D	Q4	10 yrs		adjusted/HR	1.13	0.80, 1.59	
				Primary-All-Cause Mortality	25(OH)D	per 10nmol/L	10 yrs	633/8329	adjusted/HR	0.95	0.92, 0.99	0.005
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.041
					25(OH)D	Q2	10 yrs		adjusted/HR	0.79	0.64, 0.98	
					25(OH)D	Q3	10 yrs		adjusted/HR	0.81	0.65, 1.01	
					25(OH)D	Q4	10 yrs		adjusted/HR	0.73	0.57, 0.92	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Skaaby et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Smit et al., 2012	Prospective Cohort	51–70 years; age ≥ 60 ; non-institutionalized; complete data on frailty; complete data on serum vitamin D concentrations	Not specified		Government	USA; multiple	4731/NR/53.5	69.4 (0.3)/NR	Non-Hispanic White=878; Non-Hispanic Black=60; Race_other1=17; Race_other2=45	Malnourished/frailty; Other; pre-frail, not frail	not frail: 71.9 ± 0.9 nmol/l pre-frail: 65.6 ± 1.1 nmol/l frail: 60.4 ± 2.3 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Smit et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race-Ethnicity, Gender, Education; Anthropometrics- BMI; Medical Conditions- Chronic Disease Index; Sun Exposure- Latitude; Smoking, Other Lifestyle Factors- Smoking	Primary-Mortality	25(OH)D	Quartile 1: <49.5 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.98	2.01, 4.42	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.37	1.44, 3.89	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.5	1.48, 4.21	
					25(OH)D	Quartile 4: >84.1 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	1.43	0.83, 2.46	
					25(OH)D	Quartile 1: <49.5 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.97	1.61, 2.40	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.62	1.29, 2.03	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.51	1.16, 1.97	
					25(OH)D	Quartile 4: >84.1 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.82	1.41, 2.35	
					25(OH)D	Quartile 1: <49.5 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.25	0.97, 1.60	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.2	0.96, 1.49	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.11	0.88, 1.40	
					25(OH)D	Quartile 4: >84.1 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Smit et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	N	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Solomon et al., 2010	Nested Case Control	Pooled nested case-control study included data from the following cohort studies: the ATBC Study; CLUE; NYU-WHS; MEC; PLCO; SWHS and SMHS.	Not specified	Cohort Consortium Vitamin D Pooling Project of Rarer Cancers	Government	Multiple Countries	2285/2282/33.5	median: 62 (controls)/IQR: 57–67 (controls)	Non-Hispanic White=821; Non-Hispanic Black=42; Asian=100; Race_other1=26	Not Reported	<37.5 nmol/L 25(OH)D - cases: 19.3%, controls: 27.5% <25 nmol/L 25(OH)D - cases: 12.1%, controls: 10.6%

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Solomon et al., 2010	Nested Case Control	age, race/ethnicity, sex, cohort, and date of blood draw	Demographics (Age, Sex, Race/Ethnicity)- Age, Race/Ethnicity, Sex; Anthropometrics- BMI; Medical Conditions- Diabetes; Sun Exposure-; Smoking, Other Lifestyle Factors- Smoking; Other - Date Of Blood Draw	Primary-Pancreatic Cancer	25(OH)D	<25nmol/L	NR	115/256	adjusted/OR	1	reference	
					25(OH)D	25<37.5nmol/L	NR	164/389	adjusted/OR	1.04	0.74, 1.44	
					25(OH)D	37.5<50.0nmol/L	NR	208/494	adjusted/OR	1.1	0.79, 1.55	
					25(OH)D	50.0<75.0nmol/L	NR	306/764	adjusted/OR	1.06	0.76, 1.48	
					25(OH)D	75.0<100.0nmol/L	NR	120/310	adjusted/OR	1.08	0.73, 1.59	
					25(OH)D	<=100nmol/L	NR	39/69	adjusted/OR	2.24	1.22, 4.12	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Solomon et al., 2010	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	N	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sorensen et al., 2012	Nested Case Control	gave birth in Norway between 1992 and 1994; n available serum sample of sufficient quality for 25-OH D analysis	Not specified		Government	Norway	328/328/49	9.0 (3.6)/NR		Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sorensen et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Sex; Sun Exposure- Season Of Blood Sample	Primary-Type 1 Diabetes	25(OH)D	<=54nmol/L-Offspring of pregnant women	NR	39/94	Adjusted/OR	2.38	1.12, 5.07	
					25(OH)D	>54 and <=59nmol/L-Offspring of pregnant women	NR	31/88	Adjusted/OR	1.78	0.85, 3.74	
					25(OH)D	>69nmol/L and 89nmol/L-Offspring of pregnant women	NR	22/75	Adjusted/OR	1.35	0.63, 2.89	
					25(OH)D	>89nmol/L-Offspring of pregnant women	NR	17/71	Adjusted/OR	1	reference	0.031

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sorensen et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	Y	B	1st reviewer comment for grade C: No sample size calculation, rationale for model (or factors controlled for), no information on blinding

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Suila et al., 2012	RCT/CCT	born at term; birth weight appropriate for gestational age	Not specified		Government	Finland; Helsinki	113/82/50	birth/NR		Not Reported	53 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Suila et al., 2012	RCT/CCT	NR	Other - Gender	Secondary-Cortical Bone Density	D3 Vit D3 1600 IU/day		29	NR (NR)	final=716 (se=7)	-8 (-12.1, -3.9)	.
					D3 Vit D3 1200 IU/day		28	NR (NR)	final=726 (se=7)	+2 (-2.1, 6.1)	0.34
					D3 Vit D3 400 IU/day		25	NR (NR)	final=724 (se=8)		.
				Secondary-Total And Trabecular Bone Density	D3 Vit D3 1600 IU/day		29	NR (NR)	final=430 (se=12)	-18 (-25, -11)	.
					D3 Vit D3 1200 IU/day		28	NR (NR)	final=451 (se=12)	+3 (-4, 10)	0.39
					D3 Vit D3 400 IU/day		25	NR (NR)	final=448 (se=13)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Suila et al., 2012	RCT/CCT	Y	ND	ND	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Sun et al., 2012	Nested Case Control	19–50 years; 51–70 years; female; registered nurses; aged 30–55	Missing 25(OH)D data	Nurses' Health Study	Government	USA; multiple	928/928/100	60.8 (5.9)/NR	Non-Hispanic White=976		Cases- 55.0(25.5) nmol/L; Control-56.8(22.7) nmol/L	

Main Analyses													
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val	
Sun et al., 2012	Nested Case Control	date and age at blood draw, menopausal status, use of postmenopausal hormone, race, smoking status	Anthropometrics- BMI; Medical Conditions- History Of Chronic Conditions, High Cholesterol; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption; Other - EGFR, C-Reactive Protein	Primary-Ischemic Stroke	25(OH)D	9.2–45.7 nmol/l	17 yrs	171/325	Adjusted/HR	1.49	1.01, 2.18	0.04	
					25(OH)D	45.8–65.4 nmol/l	17 yrs	160/314	Adjusted/HR	1.26	0.89, 1.79		
					25(OH)D	66.5–264.3 nmol/l	17 yrs	133/289	Adjusted/HR	1	Reference		

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sun et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Szulc et al., 2009	Prospective Cohort	51–70 years; men; age 50–85	none	MINOS study	Manufacturer	Montceau les Mines, France	782/782/0	64 (7)/NR		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Szulc et al., 2009	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Vitamin D Supplementation; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- Health Status; Smoking, Other Lifestyle Factors- Smoking, Physical Performance And Activity	Primary-Mortality	25(OH)D	per SD decrease	10 yrs	600/782	adjusted/HR	1.22	1.01, 1.48	
					25(OH)D	Quartile 1 <65 nmol/l summer or <40 nmol/l other months	10 yrs	NR/NR	adjusted/HR	1.44	1.03, 2.03	
					25(OH)D	Quartiles 2–4	10 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Szulc et al., 2009	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	Y	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Szulc et al., 2009	Prospective Cohort	51–70 years; men; age 50–85 years	Not specified	MINOS study	Unclear	Montceau les Mines, France	681/NR/0	64 (7)/NR		Not Reported	25(OH)D alive: 70.8 ± 28.8 nM deceased: 57.5 ± 27.5 nM

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Szulc et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- History Of Ischemic Heart Disease, Arterial Hypertension, Stroke, Parkinson's Disease, Diabetes Mellitus, Pulmonary Diseases, Gastrointestinal And Liver Diseases, Prostate Cancer; Smoking, Other Lifestyle Factors- Smoking, Alcohol Intake, Professional Physical Activity, Leisure Physical Activity, Physical Performance Score; Other - Aortic Calcification Score (ACS), Serum 17be2	Primary-Mortality	25(OH)D	Quartile 1	10 yrs	NR/NR	adjusted/HR		NR	<0.05
					25(OH)D	Quartiles 2–4	10 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Szulc et al., 2009	Y	Y	Y	N				Y	N	N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Thornton et al., 2013	Prospective Cohort	3–8 years; 9–18 years; age 5–12 years; enrolled in the public primary school system	Not specified	Bogotá School Children Cohort	Unclear	Bogota, Columbia	475/475/52	8.9 (1.6)/NR		Other; ~7–12.5% stunted	25(OH)D: 73.2 ± 19.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Thornton et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex	Primary-Earache/Discharge With Fever	25(OH)D	Deficient: <50	140 days	nr/48	adjusted/RR	2.36	1.26, 4.44	
					25(OH)D	Insufficient: 50–<75	140 days	nr/222	adjusted/RR	0.35	0.19, 0.65	
					25(OH)D	Sufficient: ≥75	140 days	nr/205	adjusted/RR	1	Reference	
				Primary-Cough With Fever	25(OH)D	Deficient: <50	140 days	nr/48	adjusted/RR	0.77	0.57, 1.04	
					25(OH)D	Insufficient: 50–<75	140 days	nr/222	adjusted/RR	0.53	0.44, 0.65	
					25(OH)D	Sufficient: ≥75	140 days	nr/205	adjusted/RR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Thornton et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	N	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Tolppanen et al., 2013	Prospective Cohort	3–8 years; 9–18 years; children from the single and twin births from pregnant women expected to give birth between 1 April 1991 and 31 December 1992; women (mothers) had to be resident in Avon while pregnant, those who left shortly after enrollment were omitted from further follow-up	Not specified	Avon Longitudinal Study of Parents and Children	Government	UK; South West England	14,062/3323/47.9	9.84 (SE: 0.02)/NR	Non-Hispanic White=936; Race_other1=65	Not Reported	serum 25OHD3: 24.9 ng/ml (SE: 0.01) serum 25OHD2: 1.4 ng/ml (IQR: 0.5–2.8)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Tolppanen et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Serum Concentrations Of Other Hormones Or Metabolites That Are Related To Vitamin D Homeostasis; Demographics (Age, Sex, Race/Ethnicity)- Ethnicity; Anthropometrics- BMI; Sun Exposure- Season, Time Spent Outdoors During Summer, Protection From Ultraviolet B Exposure; Other - Head Of Household Social Class, Mother's And Partner's Education	Primary-Wheezing	25(OH)D2	per doubling of exposure	1 yrs	141/3323	adjusted/OR	0.83	0.68, 1.00	
					25(OH)D3	per doubling of exposure	1 yrs	141/3323	adjusted/OR	1.14	1.03, 1.28	
				Primary-Asthma	25(OH)D2	per doubling of exposure	1 yrs	464/3323	adjusted/OR	0.89	0.78, 1.02	
					25(OH)D3	per doubling of exposure	1 yrs	464/3323	adjusted/OR	1.02	0.93, 1.12	
				Primary-Flexural Dermatitis	25(OH)D2	per doubling of exposure	1 yrs	300/3748	adjusted/OR	0.83	0.72, 0.94	
					25(OH)D3	per doubling of exposure	1 yrs	300/3748	adjusted/OR	1.09	1.00, 1.18	
				Primary-Fvc	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0.04	0.00, 0.09	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.03, 0.03	
				Primary-Fev	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0.06	0.01, 0.10	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.03, 0.03	
				Primary-Fef	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.01, 0.01	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome		-0.01, 0.00	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Tolppanen et al., 2013	Y	Y	Y	N				Y	N	

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	N	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Tomson et al., 2013	Prospective Cohort	19–50 years; 51–70 years; non-industrial Civil Servants; male; age 40–64 years	Not specified	Whitehall study	Private Foundation	UK; London	5409/5409/0	76.9 (4.9)/NR		Other; self-reported health good/excellent 77.4%	median 25(OH)D 56 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Tomson et al., 2013	Prospective Cohort	NR	Anthropometrics- Body Mass Index;; Medical Conditions- Recall Of A Diagnosis Of Ischaemic Heart Disease, Stroke, Cancer, Or Diabetes, Plus Self-Reported Health/Frailty; Smoking, Other Lifestyle Factors- Smoking Status, Drinking Status; Other - LDL-C, HDL-C, Apolipoprotein A1, Apolipoprotein B, And Blood Pressure, Albumin, Fibrinogen, And C-Reactive Protein, Estimated Glomerular Filtration Rate	Primary-Death, Ischemic Heart Disease	25(OH)D	Doubling Concentration	13.1 yrs	659/5409	adjusted/HR	0.84	0.70, 1.02	
				Primary-Death, Stroke	25(OH)D	Doubling Concentration	13.1 yrs	378/5409	adjusted/HR	0.81	0.63, 1.03	
				Primary-Death, Other Vascular	25(OH)D	Doubling Concentration	13.1 yrs	321/5409	adjusted/HR	0.71	0.54, 0.93	
				Primary-Death, All Vascular	25(OH)D	Doubling Concentration	13.1 yrs	1358/5409	adjusted/HR	0.8	0.70, 0.91	
				Primary-Death, Cancer	25(OH)D	Doubling Concentration	13.1 yrs	809/5409	adjusted/HR	0.84	0.71, 1.00	
				Primary-Death, All Non-Vascular	25(OH)D	Doubling Concentration	13.1 yrs	1857/5409	adjusted/HR	0.77	0.69, 0.86	
				Primary-Death, All Causes	25(OH)D	Doubling Concentration	13.1 yrs	3215/5409	adjusted/HR	0.78	0.72, 0.85	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Tomson et al., 2013	Y	N	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	N	NA	Y	N	N	B	should get references 21, 22 to check eligibility and sampling --- Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Toxqui et al., 2013	RCT/CCT	9–18 years; 19–50 years; Healthy; 18–35 years old; non-smoking; non-pregnant; non-breastfeeding	iron metabolism related diseases; amenorrhea; menopause; chronic gastritis, renal disease or blood donor status; allergy to dairy components		Government	Spain	165/109/100	26.5 (3.8)/NR	Non-Hispanic White=100		Serum: D-placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Toxqui et al., 2013	RCT/CCT	NR	NR	Secondary-Systolic Blood Pressure	D 200 IU/day		55	109.3 (sd=10.4)	final=105.9 (sd=9.1)	-2.4 (-5.9, 1.1)	0.178
					D placebo		54	107.7 (sd=11.7)	final=108.3 (sd=9.4)	.	
				Secondary-Diastolic Blood Pressure	D 200 IU/day		55	67.1 (sd=8.3)	final=66.6 (sd=7.3)	-0.1 (-2.9, 2.7)	0.944
					D placebo		54	69.2 (sd=9.4)	final=66.7 (sd=7.5)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Toxqui et al., 2013	RCT/CCT	ND	ND	ND	Y	ND	N	Y	N	Y	B	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Travis et al., 2009	Nested Case Control	19–50 years; 51–70 years; center-specific criteria	Not specified	European Prospective Investigation into Cancer and Nutrition (EPIC)	Government	Multiple Countries	1404/1404/0	60.5 (6.2)/NR		Not Reported	Serum 25OHD controls: 53.5 nmol/L, 95% CI (51.9, 55.1) cases: 53.6 nmol/L, 95% CI (52.0, 55.3)	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Travis et al., 2009	Nested Case Control	study center, age at enrollment (66months), time of day of blood collection (61 hour), and time between blood draw and last consumption of food or drink (<3, 3–6,>6 hours; for Umea, Sweden <4, 4–8, >8 hours)	Demographics (Age, Sex, Race/Ethnicity)- Education; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking Status, Alcohol Intake, Physical Activity	Primary-Prostate Cancer	25(OH)D	Quintile 1 (2.5–40.4nmol/L)	4.1 years	125/276	adjusted/OR	1	reference	
					25(OH)D	Quintile 2(40.5–50.4 nmol/L)	4.1 years	143/293	adjusted/OR	1.27	0.89, 1.81	
					25(OH)D	Quintile 3(50.5–59.1nmol/L)	4.1 years	128/279	adjusted/OR	1.23	0.85, 1.76	
					25(OH)D	Quintile 4 (59.2–70.8nmol/L)	4.1 years	114/269	adjusted/OR	1.06	0.73, 1.55	
					25(OH)D	Quintile 5(70.9–163.7nmol/L)	4.1 years	142/292	adjusted/OR	1.28	0.88, 1.88	
					25(OH)D	Doubling Concentration	4.1 years	652/1404	adjusted/OR	1.17	0.93, 1.47	0.188

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Travis et al., 2009	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Virtanen et al., 2011	Prospective Cohort	51–70 years	Current cancer; Current cardiovascular disease; those without information on stroke history; those without data on serum 25(OH)D	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study	Government	Finland	1136/1136/51.4	61.8 (6.2)/53.4–72.7		Post menopausal; Other; 54–62% hypertension	Serum 25OHD: 43.7 ± 17.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Virtanen et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education Years; Anthropometrics- BMI; Medical Conditions- Diabetes, Treated Hypertension; Smoking, Other Lifestyle Factors- Smoking; Other - Medication For Hyperlipidemia	Primary-Mortality	25(OH)D	Tertile 1: 8.9–34.0 nmol/L	9.1 yrs	39/379	adjusted/HR	2.06	1.12, 3.80	0.02
					25(OH)D	Tertile 2: 34.1–50.8 nmol/L	9.1 yrs	31/378	adjusted/HR	1.68	0.92, 3.07	
					25(OH)D	Tertile 3: 50.9–112.8 nmol/L	9.1 yrs	17/379	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Virtanen et al., 2011	Y	Y	N	Y				N	Y	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wagner et al., 2013	RCT/CCT	Pregnant or lactating women; age 16 years or greater; confirmed singleton pregnancy of less than 16 weeks; intent to receive prenatal care throughout pregnancy	Other systemic bone disease (e.g., Paget's); requirement for chronic diuretic or cardiac medication; active thyroid disease		Private Foundation	USA	504/1008/100	27/18–41	Non-Hispanic White=327; Hispanic=409; Non-Hispanic Black=255; Not reported=09		61.5 nmol/L

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wagner et al., 2013	RCT/CCT	Not relevant	Demographics (Age, Sex, Race/Ethnicity)- Race	Primary-	D3	2000 IU	NR	9/201	unadjusted/RR	0.55	0.22, 1.34	0.43
					D3	4000 IU	NR	4/193	unadjusted/RR	0.25	0.08, 0.80	0.05
						control	NR	9/110	unadjusted/RR	1	reference	

Main Analyses (Continuous Outcomes)											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Wagner et al., 2013	RCT/CCT	Not relevant	Demographics (Age, Sex, Race/Ethnicity)- Race	Secondary-Neonatal Birth Weight	D3 2000 IU		201	()	final=3382 (sd=759)	+149 (-21, 319)	0.09
					D3 4000 IU		193	()	final=3231 (sd=632)	-2 (-154, 150)	0.98
					control		110	()	final=3233 (sd=668)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wagner et al., 2013	RCT/CCT	N	Y	NA	N	Y	N	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wamberg et al., 2013	RCT/CCT	9–18 years; 19–50 years; Healthy; age 18–50 years; BMI>30; plasma 25(OH) vitamin D<50 nmol/L	Type 2 DM; fasting plasma glucose>7.;; hypercalcemia; impaired renal function (plasma creatinine>130umol/L; impaired hepatic function (alanine aminotransferase >135U/L; history of sarcoidosis, nephrolithiasis, osteomalacia; alcohol or other substance abuse; recent major weight changes,(+/-3 kg) or body weight>125 kg; vitamin D treatment within prior 3 months		Unclear	Denmark	52/43/73	41.2 (6.8)/18–50		Overweight/obese	34.6±10.3 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Wamberg et al., 2013	RCT/CCT	Not relevant but arms were balanced with respect to sex, age, bod weight, BMI, blood pressure, fasting glucose, physical activity, dietary baseline vitamin D intake, and plasma 25(OH)D.	NR	Secondary-Systolic Blood Pressure	D 7000 IU cholecalciferol		22	135 (sd=18)	final=129 (sd=13)	-2 (-11, 7)	0.65
					placebo		21	132 (sd=15)	final=131 (sd=16)		.
				Secondary-Diastolic Blood Pressure	D 7000 IU cholecalciferol		22	85 (sd=10)	final=84 (sd=11)	0 (-7, 7)	1
					placebo		21	81 (sd=10)	final=84 (sd=11)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wamberg et al., 2013	RCT/CCT	Y	ND	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics												
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status	
Wang et al., 2013	Prospective Cohort	19–50 years; 51–70 years; Healthy; Male physicians; 40–84 years of age	Prior cancer; Current cancer; Current cardiovascular disease; Hypertension; chronic disease	Physicians' Health Study (PHS)	Government	USA	660/660/0	57.6 (7.6)/40–84			Winter/spring: 55.9±22.5 Summer/fall: 77.4±26.2	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wang et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking (Never, Past, Current), Alcohol Use, Vigorous Exercise; Other - History Of Hyperlipidemia	Primary- Hypertension	25(OH)D	Q1: 13.0–57.8	15.3 yrs	97/164	adjusted/HR	1	Reference	0.43
					25(OH)D	Q2: 37.0–74.9	15.3 yrs	97/164	adjusted/HR	0.94	0.69, 1.27	
					25(OH)D	Q3: 48.6–93.5	15.3 yrs	79/167	adjusted/HR	0.67	0.50, 0.96	
					25(OH)D	Q4: 68.8–167.2	15.3 yrs	94/165	adjusted/HR	0.82	0.60, 1.13	
					25(OH)D	<50	15.3 yrs	73/136	adjusted/HR	1	Reference	0.32
					25(OH)D	50–74	15.3 yrs	144/244	adjusted/HR	1.03	0.75, 1.42	
					25(OH)D	75–99	15.3 yrs	93/178	adjusted/HR	0.79	0.56, 1.11	
					25(OH)D	>=100	15.3 yrs	57/102	adjusted/HR	0.94	0.62, 1.40	
					1,25(OH)D	Q1: 29.9–79.3	15.3 yrs	87/162	adjusted/HR	1	Reference	0.16
					1,25(OH)D	Q2: 68.0–88.2	15.3 yrs	80/162	adjusted/HR	0.92	0.66, 1.27	
					1,25(OH)D	Q3: 80.8–101.8	15.3 yrs	95/165	adjusted/HR	1.12	0.82, 1.54	
					1,25(OH)D	Q4: 94.0–177.6	15.3 yrs	101/162	adjusted/HR	1.19	0.86, 1.63	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wang et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ward et al., 2010	RCT/CCT	9–18 years; Healthy; postmenarchal girls; attended an inner-city, multiethnic, all-girls school in Manchester UK	Pregnant; evidence of liver, kidney, or other disorders that may cause nonnutritional vitamin D deficiency or abnormal bone development; clinical signs of vitamin D deficiency		Government	UK; Manchester	72/65/100	13.8 (0.7)/12–14			total serum 25OHD placebo: 17.9 ± 7.4 nmol/l vit D group: 18.1 ± 8.0 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Ward et al., 2010	RCT/CCT	NR	Anthropometrics- Follow-Up Height, Baseline And Follow-Up Weight	Secondary-Maximum Force	Vit D2 150,000 IU/ quarterly		33	2.80 (SD=0.23)	change= -0.08 (SD=0.22)	-0.04 (-0.12, 0.04)	0.32
					Placebo		32	2.71 (SD=0.32)	change= -0.04 (SD=0.04)		.
				Secondary-Eslinger Fitness Index	Vit D2 150,000 IU/ quarterly		33	89.44 (SD=14.41)	change= -4.31 (SD=9.32)	+0.17 (-3.8, 4.2)	0.93
					Placebo		32	85.41 (SD=15.57)	change= -4.48 (SD=6.68)		.
				Secondary-Efficiency	Vit D2 150,000 IU/ quarterly		33	87.76 (SD=13.00)	change= 2.72 (SD=8.57)	+1.10 (-0.91, 3.12)	0.1
					Placebo		32	84.36 (SD=14.31)	change= -0.56 (SD=7.42)		.
				Secondary-Velocity	Vit D2 150,000 IU/ quarterly		33	2.19 (SD=0.21)	change= 0.02 (SD=0.13)	+0.03 (-0.03, 0.09)	0.28
					Placebo		32	2.12 (SD=0.24)	change= -0.01 (SD=0.09)		.
				Secondary-Jump Height	Vit D2 150,000 IU/ quarterly		33	0.34 (SD=0.06)	change= 0.01 (SD=0.04)	+0.01 (-0.01, 0.03)	0.32
					Placebo		32	0.33 (SD=0.06)	change= 0.00 (SD=0.04)		.
				Secondary-Maximum Power Relative To Body Weight	Vit D2 150,000 IU/ quarterly		33	39.52 (SD=6.21)	change= -1.06 (SD=4.18)	+0.18 (-1.6, 2.0)	0.84
					Placebo		32	37.81 (SD=6.81)	change= -1.24 (SD=2.91)		.
				Secondary-Spine Bone Mineral Content (BMC)	Vit D2 150,000 IU/ quarterly		35	11.73 (SD= 1.99)	change= 0.52 (SD=0.39)	-0.05 (-0.24, 0.15)	0.62
					Placebo		33	11.97 (SD= 1.97)	change= 0.57 (SD=0.43)		.
				Secondary-Tibia 66% Cortical Bone Mineral Content (Ct BMC)	Vit D2 150,000 IU/ quarterly		33	268.38 (SD= 38.85)	change= 7.68 (SD=12.26)	-1.98 (-8.4, 4.4)	0.54
					Placebo		31	261.23 (SD= 38.06)	change= 9.66 (SD=13.38)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization (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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Ward et al., 2010	RCT/CCT	Y	Y	ND	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wei et al., 2012	Prospective Cohort	Pregnant or lactating women; between 12 and 18 completed weeks of pregnancy on the basis of last menstrual period and confirmed by early ultrasound examination	women who had a history of medical complications including endocrine disease (e.g., thyroid disease), renal disease with altered renal function, epilepsy, any collagen vascular disease (e.g., systemic lupus erythematosus and scleroderma), active and chronic I; regularly consumed supplements 200 mg/day for vitamin C and/or 50 IU/day for vitamin E; took warfarin; women who had known fetal abnormalities (e.g., hydatidiform mole), or known fetal chromosomal or major malformations in the current pregnancy; women with repeated spontaneous abortion (women with a previous bleeding in the first trimester were included if the site documented a viable fetus at the time of recruitment; women who used an illicit drug during the current pregnancy	International Trial of Antioxidants in the Prevention of Pre-eclampsia (INTAPP)	Government	Canada	697/697/100	30.3 (4.8)/NR	Non-Hispanic White=892; Not reported=118	Other; 31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of pre-eclampsia	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wei et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Prepregnancy BMI; Medical Conditions- Risk Group (See Comments); Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking	Primary- Preeclampsia	25(OH)D	per SD increase	12–18 weeks gestation	32/697	adjusted/OR	0.79	0.52, 1.20	NR
					25(OH)D	<50	12–18 weeks gestation	15/272	adjusted/OR	1.24	0.58, 2.67	NR
					25(OH)D	>50	12–18 weeks gestation	17/425	adjusted/OR	1	Reference	NR
					25(OH)D	per SD increase	24–26 weeks gestation	28/604	adjusted/OR	0.68	0.44, 1.05	NR
					25(OH)D	<50	24–26 weeks gestation	19/236	adjusted/OR	3.24	1.37, 7.69	NR
					25(OH)D	>50	24–26 weeks gestation	9/368	adjusted/OR	1	Reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wei et al., 2012	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wei et al., 2013	Prospective Cohort	Pregnant or lactating women; 12–18 weeks gestation	Current cardiovascular disease; use of warfarin; use of vitamin C or vitamin E prior to main intervention; collagen vascular disease; carrying a fetus with a known abnormality; endocrine disease; renal disease; epilepsy; use of an illicit drug during pregnancy; active or chronic liver disease; repeated spontaneous abortion	INTAPP	Government	Canada	697/NR/100	28.68 (5.44)/NR	Non-Hispanic White=3400; Hispanic=3484 ; Non-Hispanic Black=134; Asian=135; Race_other1= 2337; Race_other2= 042		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wei et al., 2013	Prospective Cohort	not relevant	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking; Other - Preeclampsia Risk Status	Primary- Preeclampsia	25(OH)D	<50 nmol/L	24–26 weeks gestation	NR/NR	adjusted/OR	2.97	1.23, 7.20	
					25(OH)D	>=50 nmol/L	24–26 weeks gestation	NR/NR	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wei et al., 2013	N	Y	Y	N						N

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	N	NA	Y	N	N	B		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Welsh et al., 2012	Prospective Cohort	19–50 years; 51–70 years; offspring of married couples in the Renfrew/Paisley cohort; aged 30–59 years; living locally	problematic addresses (addresses provided by parents or death certificate informants which, for reasons of completeness or accuracy, could not be located in a current postcode directory); died before study commenced	MIDSPAN Family Study	Private Foundation	UK; Renfrew and Paisley	2081/1492/54 %	45.2 (6.2)/NR	Non-Hispanic White=100	Vitamin d deficient/depleted; Other; vitamin D not deficient	serum 25OHD vitamin D not deficient group (=15 ng/ml); 22.9 ng/ml vitamin D deficient group (<15 ng/ml); 11.0 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Welsh et al., 2012	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Percent Fat From Diet, High And Low Fiber In Diet, Vitamin D Intake, Adjusted Calcium; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Highest Educational Level, Social Class, Deprivation Category; Anthropometrics- BMI, Waist Circumference; Medical Conditions- Diabetes, Baseline Coronary Heart Disease; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking, Alcohol Intake, Low Baseline Physical Activity; Other - Systolic Blood Pressure, HDL And Total Cholesterol, Current Medication (Ace Inhibitors, Antihypertensives, Aspirin, Insulin, Oral Hypoglycemic, Spartans, Statins)	Primary-All-Cause Mortality	25(OH)D	per 1 SD increase	14.4 yrs	70/1492	adjusted/HR	0.74	0.56, 0.99	
					25(OH)D	Deficient, <15 ng/ml	14.4 yrs	NR/689	adjusted/HR	2.02	1.17, 3.51	
					25(OH)D	Not deficient ≥15 ng/ml	14.4 yrs	NR/803	adjusted/HR	1	reference	
				Primary-Cardiovascular Event	Dietary Vit D intake	per 1 SD increase in dietary Vit D intake-log scale	14.4 yrs (median)	293/1492	Adjusted/HR	0.94	0.83, 1.08	NR
					25(OH)D	per 1 SD increase in 25(OH)D-log scale	14.4 yrs (median)	293/1492	Adjusted/HR	1.07	0.94, 1.23	NR
					25(OH)D	<15ng/ml	14.4 yrs (median)	293/1492	Adjusted/HR	1	0.77, 1.31	NR
					25(OH)D	≥15 ng/ml	14.4 yrs (median)		Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Welsh et al., 2012	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Witham et al., 2013	RCT/CCT	9–18 years; 19–50 years; 51–70 years; age 18 or over; serum 25(OH)D<75; female; South Asian origin	any except fish oil; symptomatic; estimated GFR<40; Liver function tests more than 3-fold upper limit of normal; adjusted serum calcium>2.60 or <2.15 mmol/L; History of renal calculi; sarcoidosis or metastatic malignancy; childbearing age and not using birth control		University	UK	50/50/100	39.4 (11.8)/NR	Race_other1=100		<50 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Witham et al., 2013	RCT/CCT	Not relevant	Other Nutrients Or Dietary Factors- Baseline 25(Oh)d; Anthropometrics- BMI; Other - Flow Mediated Dilation, PTH, Total Cholesterol	Secondary-Systolic Blood Pressure	D3 100,000 units		25	119 (sd=15)	change=2.0 (sd=7.9)	+3.0 (-1.9, 8.0)	.
					D3 placebo		25	122 (sd=19)	change=-1.0 (sd=9.1)		.
				Secondary-Diastolic Blood Pressure	D3 100,000 units		25	78 (sd=11)	change=-0.1 (sd=5.7)	+0.6 (-2.5, 3.7)	.
					D3 placebo		25	78 (sd=13)	change=-0.7 (sd=5.2)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Witham et al., 2013	RCT/CCT	Y	Y	NA	Y	ND	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wong et al., 2013	Prospective Cohort	51–70 years; 65 years and older	Not specified		Government	Australia;Perth	4203/4203/0	76/70–88		Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wong et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- Cardiovascular Disease, Diabetes, Hypertension, Dyslipidemia, Charlson's Comorbidity Index, Renal Function; Smoking, Other Lifestyle Factors- Smoking; Other - Season, Baseline Frailty Status	Primary-All-Cause Mortality	25(OH)D	per 10nmol/L decrease in 25(OH)D	6.7 yrs	1144/4203	adjusted/HR	1.04	1.01, 1.07	
					25(OH)D	halving of 25(OH)D	6.7 yrs		adjusted/HR	1.21	1.08, 1.35	
					25(OH)D	Q1: 10–52.8	6.7 yrs		adjusted/HR	1.2	1.02, 1.42	
					25(OH)D	Q2: 52.9–67.3	6.7 yrs		adjusted/HR	1	Reference	
					25(OH)D	Q3: 67.4–81.6	6.7 yrs		adjusted/HR	0.99	0.84, 1.17	
					25(OH)D	Q4: 81.7–238.4	6.7 yrs		adjusted/HR	0.99	0.83, 1.17	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wong et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	N	NA	Y	N	N	B	ref 18: http://ije.oxfordjournals.org/content/38/1/48.full.pdf+html	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wood et al., 2012	RCT/CCT	Postmenopausal women; Caucasian	CVD; diabetes, asthma, malabsorption, hypertensive blood pressure measurements of at least 160 mm Hg systolic or 99 mm Hg diastolic; difficulty in swallowing tablets or capsules; medications or supplements known to affect any dependent variable; current smokers; abnormal blood biochemistry at screening		Government	UK; Aberdeen	305/197/100	63.9 (2.3)/NR	Non-Hispanic White=100	Post menopausal	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Wood et al., 2012	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Serum Calcium (Adjusted For Albumin), Serum Total 25(OH)d, Plasma PTH; Anthropometrics- Baseline Measurements Of Weight; Smoking, Other Lifestyle Factors- Physical Activity Level; Other - Grip Strength, Weekly Sed, Serum Calcium Concentrations, Baseline Adipose Tissue Distribution	Secondary-DBP	D3 400 IU Vit D/day		97	77.68 (sd=7.3)	change=-2.5 (-3.6, -1.4)	-0.4 (-1.9, 1.1)	.
					D3 placebo		100	77.7 (sd=7.8)	change=-2.1 (-3.1, -1.0)		.
				Secondary-SBP	D3 400 IU Vit D/day		96	128.16 (sd=13.8)	change=-2.2 (-3.3, -0.7)	+0.2 (-2.2, 2.6)	.
					D3 placebo		98	128.18 (sd=13.3)	change=-2.4 (-4.5, -0.2)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wood et al., 2012	RCT/CCT	Y	ND	Y	N	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Woodham et al., 2011	Nested Case Control	Pregnant or lactating women; previously given blood for routine genetic multiple marker screening and subsequently delivered at the University of North Carolina-Chapel Hill between Jan 2004 and Nov 2008	kidney disease, diabetes mellitus, known thrombophilias, any other significant preexisting chronic medical disease; multiple gestation; major congenital fetal anomalies; pregestational hypertension		Government	UK; Chapel Hill	164/164/100	median: 29/IQR: 25–33	Non-Hispanic White=29; Hispanic=27; Non-Hispanic Black=39; Asian=5	Not Reported	Serum 25(OH)D - median (IQR) controls: 107 (90–121) nmol/l cases: 75 (53–107) nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Woodham et al., 2011	Nested Case Control	race/ethnicity	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Blood Draw, Silt-1/Plgf Ratio [soluble Fms-Like Tyrosine Kinase-1, Placental Growth Factor]	Primary-Severe Preeclampsia	25(OH)D	NR	NR	41/164	adjusted/OR	0.95	0.94, 0.97	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Woodham et al., 2011	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Woolcott et al., 2010	Nested Case Control	51–70 years; age 45–75 years	Not specified	Multiethnic Cohort	Government	USA; Hawaii, Los Angeles	633/663/35.9 (controls)	69.2 (7.9)/NR	Non-Hispanic White=171; Non-Hispanic Black=187; Race_other1=394; Race_other2=88; Race_other3=46	Not Reported	Plasma 25(OH)D controls: 25.0 ± 9.9 ng/ml cases: 23.2 ± 10.1 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Woolcott et al., 2010	Nested Case Control	sex, race/ethnicity, study area, data (± 6 mo) and time (± 2 h) between blood draw and case diagnosis, birth year (± 1 y), hours fasting before blood draw (8 to <10 h, =10 h)	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Other - Data And Time Of Blood Draw, Hours Fasting, Family History Of Colon Cancer, Intake Of Processed Red Meat	Primary-Colorectal Cancer	25(OH)D	<16.8 ng/mL	NR	67/154	adjusted/OR	1	reference	
					25(OH)D	16.8 <22.2 ng/mL	NR	42/128	adjusted/OR	0.63	0.37, 1.08	
					25(OH)D	22.2 <26.3 ng/mL	NR	38/126	adjusted/OR	0.54	0.32, 0.93	
					25(OH)D	26.3 <32.8 ng/mL	NR	43/130	adjusted/OR	0.62	0.36, 1.07	
					25(OH)D	≥ 32.8 ng/mL	NR	39/125	adjusted/OR	0.6	0.33, 1.07	
					25(OH)D	Per doubling	NR	NR/663	adjusted/OR	0.68	0.51, 0.92	0.010

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Woolcott et al., 2010	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies										
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup $<20\%$?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)	
Y	Y	Y	Y	Y	Y	N	N	A		

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Zhu et al., 2008	RCT/CCT	9–18 years; age 10 years; girls	Not specified		Manufacturer	China; Beijing	757/235/100	10.1 (0.3)/NR			Vit D intake Control group – 0.9 ± 0.6µg/d CaD milk – 0.9 ± 0.6µg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Zhu et al., 2008	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Ca Intake, Vitamin D Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Height, Weight; Other - Tanner Breast Stage, Tanner Pubic Hair Stage, Post-Menarche	Secondary-Midriff BMD size-corrected (sc)	D3 560 mg calcium + 5–8 µg Vit D/school day		112	1585 (sd=332)	final=1803 (sd=446)	+43 (-79, 165)	.
					D3 control (no supplementary milk and habitual diet)		123	1584 (sd=337)	final=1760 (sd=499)		.
				Secondary-Pelvis BMD sc	D3 560 mg calcium + 5–8 µg Vit D/school day		112	46 (sd=4)	final=49 (sd=7)	0 (-1.9, 1.9)	.
					D3 control (no supplementary milk and habitual diet)		123	47 (sd=5)	final=49 (sd=8)		.
				Secondary-Total Body BMD sc	D3 560 mg calcium + 5–8 µg Vit D/school day		112	93 (sd=5)	final=95 (sd=10)	+3 (0.3, 5.7)	.
					D3 control (no supplementary milk and habitual diet)		123	95 (sd=6)	final=92 (sd=11)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Zhu et al., 2008	RCT/CCT	ND	ND	ND	Y	Y	ND	Y	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Zhu et al., 2010	RCT/CCT	51–70 years; age 70–90 years; plasma 25(OH)D concentration less than 24 ng/ml; history of at least one fall in the previous 12 months	current consumption of vitamin D or bone or mineral active agents apart from calcium; BMD Z-score at total hip site of less than -2.0; medical conditions or disorders that influence bone mineral metabolism; fracture in the past 6 months; Mini-Mental State Examination score less than 24 or the presence of significant neurological conditions likely to substantially impair balance or physical activity such as stroke; Parkinson's disease		Manufacturer	Australia;Perth	302/261/100	77.0 (4.8)/NR	Non-Hispanic White=970; Asian=30; Race_other1=0	Other; plasma 25(OH)D concentration less than 24 ng/mL	Serum 25(OH)D 17.7 ± 4.2 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Zhu et al., 2010	RCT/CCT	NR	NR	Secondary-Timed Up And Go (TUAG)	Vit D2 + Calcium 1,000 mg/d calk +1,00 IU vit D2		129	11.0 (SD=5.3)	Final=8.1 (SD=3.9)	-0.9 (-2.2, 0.5)	0.2
					Placebo + Calcium 1,000 mg/d calk		132	10.8 (SD=4.6)	Final=9 (SD=7)		.
				Secondary-Lower Limb Muscle Strength: Ankle Dorsiflexion	Vit D2 + Calcium 1,000 mg/d calk +1,00 IU vit D2		129	11.6 (SD=4.4)	Final=10.9 (SD=3.7)	0 (-0.9, 0.9)	1
					Placebo + Calcium 1,000 mg/d calk		132	11.8 (SD=4.2)	Final=10.9 (SD=4)		.
				Secondary-Lower Limb Muscle Strength: Knee Flexor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	11.8 (SD=3.6)	Final=12.9 (SD=3.5)	-0.1 (-1.0, 0.8)	0.83
					Placebo + Calcium 1,000 mg/d calcium		132	11.9 (SD=3.7)	Final=13 (SD=3.9)		.
				Secondary-Lower Limb Muscle Strength: Knee Extensor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	18.3 (SD=6.4)	Final=18 (SD=5)	-0.3 (-1.6, 1.0)	0.65
					Placebo + Calcium 1,000 mg/d calcium		132	18.8 (SD=7.3)	Final=18.3 (SD=5.5)		.
				Secondary-Lower Limb Muscle Strength: Hip Extensor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.6 (SD=5.7)	Final=17.2 (SD=5.2)	+0.3 (-1.1, 1.7)	0.67
					Placebo + Calcium 1,000 mg/d calcium		132	14.4 (SD=5.3)	Final=16.9 (SD=6.2)		.
				Secondary-Lower Limb Muscle Strength: Hip Abductor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	12.3 (SD=4.2)	Final=14.5 (SD=4.1)	+0.4 (-0.7, 1.5)	0.48
					Placebo + Calcium 1,000 mg/d calcium		132	12.2 (SD=5)	Final=14.1 (SD=4.9)		.
				Secondary-Lower Limb Muscle Strength: Hip Flexor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.5 (SD=5)	Final=15.4 (SD=4.2)	0 (-1.1, 1.1)	1
					Placebo + Calcium 1,000 mg/d calcium		132	14.5 (SD=5.7)	Final=15.4 (SD=4.8)		.

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-Lower Limb Muscle Strength: Hip Adductor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.4 (SD=4.7)	Final=16.4 (SD=4.2)	+0.1 (-1.1, 1.3)	0.86
					Placebo + Calcium 1,000 mg/d calcium		132	14.7 (SD=5)	Final=16.3 (SD=5.2)	.	

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Zhu et al., 2010	RCT/CCT	Y	ND	Y	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Zhu et al., 2013	RCT/CCT	19–50 years; Healthy; absence of coronary heart disease, hypertension, diabetes, dyslipidemia; BMI =24 kg/m ² or more or BMI of 28; age 18–25 years; daily calcium intake <600 mg	Pregnant; use of calcium supplements or any medication that could affect body weight within 30 days of screening, no smoking; participating in any weight loss programs or in any other clinical trial; lactation		Government	China; Shanghai	53/43/85.7%	20.3 (0.8)/NR			Habitual Ca intake CaD group - 426.5 +/- 152.2 mg/d Control group - 392.1 +/- 141.1 mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Zhu et al., 2013	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Initial Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Baseline Body Weight	Secondary-DBP	D3 (energy-restricted diet+600 mg calcium+125 IU Vit D)/day		22	70.7 (sd=7.1)	final=64.2 (sd=4.7)	-1.2 (-4.6, 2.2)	.
					D3 energy-restricted diet alone (control)		21	70 (sd=7.8)	final=65.4 (sd=6.3)		.
				Secondary-SBP	D3 (energy-restricted diet+600 mg calcium+125 IU Vit D)/day		22	119.2 (sd=10.5)	final=109.6 (sd=9.9)	-2.3 (-8.6, 4.0)	.
					D3 energy-restricted diet alone (control)		21	123 (sd=10.5)	final=111.9 (sd=10.4)		.

Quality of Interventional Studies												
Author, Year	Study 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 w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Zhu et al., 2013	RCT/CCT	Y	N	ND	Y	N	Y	Y	N	Y	B	

Appendix D. Evaluation of Existing Systematic Reviews and Evidence Tables of the Qualified Systematic Reviews

List of Acronyms and Abbreviations

Acronym/Abbreviation	Term
BP	Blood pressure
Ca	Calcium
CRC	Colorectal cancer
DBP	Diastolic blood pressure
HTN	Hypertension
im	intramuscular
NTN	Normotensive
OR	Odds ratio
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SE	Standard error

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 ^s
Included in Current Report									
Wang, 2012 Circulation Cardiovascular Quality and Outcomes [23149428]	Vitamin D (serum 25(OH)D)	Cardiovascular disease risk	Prospective	Yes and no	Not relevant	Yes	Yes	Yes	Many studies included in current or original report
Autier, 2012 J Clin Endocrinol Metab [22701014]	Vitamin D [+/- Calcium]	Serum 25(OH)D concentration	RCTs	Yes	Yes	Yes	Yes	Yes	Included a small number of studies of im administration
Included in Original Report									
Autier 2007 Arch Intern Med [17846391]**	Vitamin D [+/- Calcium]	All cause mortality	RCTs	Yes	Yes	Yes	Yes	Yes	One additional study found
Avenell 2008 Cochrane Database of Systematic Reviews [16034849]§§	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	Observ- ational, including cross- sectional	Unclear	No	NA (regressions)	Yes	No	REJECT Includes XS

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 [§]
Dickinson 2008 Cochrane	Ca supplement	Blood pressure	RCT	No All with HTN	Yes	Yes	Yes	Yes	Revision of 2006 SR 15/64 potential RCTs
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 ^s
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 ^s
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 supplementa- tion food or chemical	weight	RCTs	yes	yes	yes	yes	yes	2° analysis of RCT of calcium on bone density outcome
Lanou 2008 Nutr Rev	Calcium or dairy supplementa- tion with or without energy restriction	Weight, body fat	RCTs	nd	yes	no	yes	yes	Included both dairy and calcium supplementati on 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.

**We excluded a study on patients with congestive heart failure in our reanalysis of data from this systematic review

§§Examined only trials on falls prevention

Evidence table of systematic review of Vitamin D supplementation on serum 25(OH)D concentrations

Author Year [PMID]	Autier 2012 [22701014]
Design	Systematic review of RCTs
Population	<ul style="list-style-type: none">• Include adults 50 years and over• Exclude individuals with chronic diseases• Exclude trials of mainly non-Caucasian participants
Intervention (Exposure) and Comparator	Intervention (Exposure): <ul style="list-style-type: none">• Include vitamin D₂ or D₃ with or without calcium• Exclude other vitamin D compounds/analogs• Include oral and im supplementation• Exclude trials of fortified foods Comparator: <ul style="list-style-type: none">• Placebo or no intervention (I.e., open-label included)
Results	See text for further summary of results: <ul style="list-style-type: none">• Compared to D3, D2 was associated with lower increases in serum 25(OH)D concentration• Concomitant use of calcium and high baseline serum 25(OH)D were associated with smaller increases in serum 25(OH)D concentration
Comments	

AMSTAR			
A priori design?	Yes	Study quality assessment performed?	Yes
Two independent reviewers?	Yes	Study quality appropriately used in analysis?	NR
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 circulating 25(OH)D and Risk for Cardiovascular Disease

Evidence table of systematic review of circulating 25(OH)D and risk for cardiovascular disease			
Author Year [PMID]	Wang 2012 [23149428]		
Design	Systematic review of prospective studies and nested case control studies		
Population	<ul style="list-style-type: none">Exclude studies of individuals with confirmed health conditions		
Intervention (Exposure) and Comparator	Intervention (Exposure): <ul style="list-style-type: none">Include only studies that assessed serum 25(OH)D concentrations Comparator: <ul style="list-style-type: none">Individuals with different serum concentrations of 25(OH)D		
Results	See text for further summary of results: <ul style="list-style-type: none">Baseline circulating 25(OH)D was associated with decreased risk for cardiovascular disease in many but not all studies		
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/No	Conflicts of interest stated?	Yes
Study characteristics provided?	Yes		

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	<ul style="list-style-type: none"> • 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	<p>Intervention (Exposure):</p> <ul style="list-style-type: none"> • Include vitamin D₂ or D₃ with or without calcium. • Exclude vitamin D preparations, calcitriol, alphacalcidol (because they are not nutritional supplements, and have different safety profile) <p>Comparator:</p> <ul style="list-style-type: none"> • No vitamin D or lower doses/levels of vitamin D
Results	<p>See text for summary results for the following outcomes in both vitamin D and combined vitamin D and calcium sections of the report:</p> <ul style="list-style-type: none"> • 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	<p>18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (\pm 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.</p>
Comments	<p>See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials.</p> <p>Study participants, vitamin D assays, and vitamin D status are not described in detail.</p>

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 reviews 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)*; 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	

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] [†]		
Design (Search Years)	Randomized controlled trials (1982-2003/2005 [‡])		
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 technical update, with no further studies added was published in the Cochrane database in 2008.

[‡] Different dates for different databases.

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 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

Blank Data Extraction Form and Quality Assessment Checklists (From the Original Report)

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 (e.g. 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) ₂ D								
		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)? Anthropometrics (e.g., BMI, body weight, % body fat)? 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) Other	Yes/no* Yes/no* Yes/no*	

*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: CONTINUOUS 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: CONTINUOUS 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 (e.g., quartiles) is given (ranges)? (y/n)	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)	applicable for categorical analyses only		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

Blank Data Extraction Form and Quality Assessment Checklists (From the Current Report)

Vitamin D Data Abstraction Form

Should this article have been previously excluded based on the exclusion criteria?

Select an Answer

- ☐ More than 20% of the population has a condition
- ☐ No outcome of interest
- ☐ Study design: Observational study of intermediate outcomes (cardiovascular and bone outcomes)
- ☐ Study design:SR/MA
- ☐ Study design other (please specify)
- ☐ Intervention: Other dietary supplements, not controlled for

[Clear Response](#)

Do you need another article to complete this form (i.e., data is reported in another article)?

- ☐ Yes (stop until the article is linked; specify reference number)
- ☐ No

[Clear Response](#)

Was this part of a trial?

We will be compiling all the studies per trial

- ☐ Yes (specify the trial name and stop)
 - ☐ No [Clear Response](#)
-

Study Design

- ☐ RCT/CCT
 - ☐ Prospective cohort
 - ☐ Nested case control
 - ☐ Post hoc
-

Population and Study Characteristics

Inclusion criteria for the study (check all that apply)

- ☐ 0-6 months
- ☐ 7 months-2 years
- ☐ 3-8 years
- ☐ 9-18 years
- ☐ 19-50 years
- ☐ 51-70 years
- ☐ ≥ 71 years
- ☐ Pregnant or lactating women
- ☐ Postmenopausal women
- ☐ Preterm newborns
- ☐ Healthy
- ☐ Persons with Osteopenia
- ☐ Able to participate, understand English..
- ☐ Other 1 (please specify)
- ☐ Other 2 (please specify)
- ☐ Other 3 (please specify)
- ☐ Other 4 (please specify)
- ☐ Other 5 (please specify)

- ☐ Other 6 (please specify)
- ☐ Other 7 (please specify)
- ☐ Not specified

Exclusion criteria for the study (check all that apply)

- ☐ Currently or previously taking vitamin d supplements (provide detail)
- ☐ Osteoporosis
- ☐ Other systemic bone disease (e.g., pagets)
- ☐ Prior fragility fracture
- ☐ Prior cancer
- ☐ Current cancer
- ☐ Current cardiovascular disease
- ☐ Hypertension
- ☐ Type 2 DM
- ☐ Pregnant
- ☐ Autoimmune disease
- ☐ Use of antihypertensives (provide details)
- ☐ Use of drugs related to bone metabolism (provide details)
- ☐ Use of medications that interfere with vitamin k (e.g., anticoagulants) (provide details)
- ☐ Consumption of dietary supplements (provide details)
- ☐ Prior cancer diagnosis (provide details)
- ☐ Prior CVD diagnosis (provide details)
- ☐ Other comorbidity(ies)(provide details)
- ☐ Other 1 (specify)
- ☐ Other 2 (specify)

- ☐ Other 3 (specify)
- ☐ Other 4 (please specify)
- ☐ Other 5 (please specify)
- ☐ Other 6 (please specify)
- ☐ Other 7 (please specify)
- ☐ Not specified

Age (indicate the mean/range/SD of the control group) **Race/Ethnicity**

- ☐ Mean age (indicate NR if not reported)
- ☐ Age range (indicate NR if not reported)
- ☐ Standard Deviation (if no age range was given)

- ☐ Non-Hispanic white (if % was given, please specify)
- ☐ Hispanic (if % was given, please specify)
- ☐ Non-Hispanic black (if % was given, please specify)
- ☐ Asian (if % was given, please specify)
- ☐ Mixed (if % was given, please specify)
- ☐ Race not specified (if % was given, please specify)
- ☐ Other_1 (specify and if % was given, please specify)
- ☐ Other_2 (specify and if % was given, please specify)
- ☐ Other_3 (specify and if % was given, please specify)
- ☐ Other_4 (specify and if % was given, please specify)
- ☐ Other_5 (specify and if % was given, please specify)
- ☐ NR (if % was given for an unknown group, please specify)

Countries

- ☐ Australia (specify city, if given)
- ☐ Canada (specify city, if given)
- ☐ China (specify city, if given)
- ☐ Finland (specify city, if given)
- ☐ Germany (specify city, if given)
- ☐ Turkey (specify city, if given)
- ☐ UK (specify city, if given)
- ☐ USA (specify city, if given)
- ☐ Multiple Countries
- ☐ Other (please specify)
- ☐ Not reported

Enrollment profile

- ☐ # Enrolled (indicate NR if not reported)
- ☐ % female (indicate NR if not reported)

Health and Nutritional status (check all that apply)

- ☐ Healthy
 - ☐ Cancer in remission
 - ☐ Osteopenia/Ibd
 - ☐ Low birth weight/sga
 - ☐ Preterm birth
 - ☐ Vitamin D
deficient/depleted
 - ☐ Overweight/obese
 - ☐ Malnourished/frailty
 - ☐ Post menopausal
 - ☐ Other
 - ☐ Not Reported
-

Baseline vitamin D/calcium intake/level (if reported, indicate “NR” if not reported)



Interventions/exposures

- ☐ Supplemental vitamin D (none specified)
- ☐ Supplemental vitamin D2
- ☐ Supplemental vitamin D3
- ☐ Supplemental Calcium
- ☐ Vitamin D fortified food (amount per serving, amount per day)
- ☐ Serum vitamin D
- ☐ Serum vitamin D status categories (high vs. low, tertiles, quartiles, quintiles)
- ☐ Cord blood vitamin D
- ☐ Other (specify)

Sources [to be used in the arms table]:

Serum

D

D2

D3

Ca

D+Ca

D2+Ca

D3+Ca

Placebo

Arm 1/ Exposure 1	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 2/ Exposure 2	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 3/ Exposure 3	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

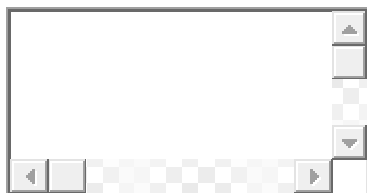
Arm 4/ Exposure 4	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 5/ Exposure 5	Source/Blo od level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Control 1	Source	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Control 2	Source	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

What characteristics were the controls and cases matched on?



What confounders were controlled for in analyses

- ☐ Other nutrients or dietary factors (specify)
 - ☐ Demographics (age, sex, race/ethnicity) (specify)
 - ☐ Anthropometrics (specify)
 - ☐ Medical conditions (specify)
 - ☐ Sun exposure (specify)
 - ☐ Smoking, other lifestyle factors (specify)
 - ☐ Other 1 (specify)
 - ☐ Other 2 (specify)
 - ☐ Other 3 (specify)
 - ☐ Other 4 (specify)
 - ☐ Other 5 (specify)
 - ☐ Other 6 (specify)
 - ☐ Other 7 (specify)
-

What were the comparators?

- ☐ Placebo
 - ☐ Not identified
 - ☐ Other vitamin d dose (specify)
 - ☐ Other (specify)
-

Compliance with treatment? (indicate % or number or indicate “NR” for not reported, and “NA” if there was no treatment)



Dose Response (check all that apply)

- ☐ Serum vitamin D
- ☐ Cord blood vitamin D

☐ Other (specify)

Autoimmune

- ☐ Colitis/Crohns
- ☐ Lupus
- ☐ Rheumatoid Arthritis

☐ Type 1 diabetes

☐ Other (specify)

Cancer

- ☐ Breast cancer
- ☐ Breast density
- ☐ Prostate cancer
- ☐ Colorectal adenoma (progression)
- ☐ Aberrant crypt cells
- ☐ Pancreatic cancer
- ☐ Any cancer mortality
- ☐ Other (specify)

Infections/Allergy/Asthma

- ☐ Infection-related mortality (specify)
 - ☐ Allergy (specify)
 - ☐ Asthma (specify)
 - ☐ Pediatric allergy (in child of woman who was subject of intervention/exposure) (specify)
 - ☐ Infectious process (specify)
 - ☐ Other (specify)
-

Bone Health

- ☐ Osteoporotic/fragility fx
 - ☐ Bone mineral density/content
 - ☐ Rickets
 - ☐ Falls
 - ☐ Muscle strength
 - ☐ Osteoporosis
 - ☐ Other (specify)
-

Cardiovascular outcomes

- ☐ Hypertension
 - ☐ Cardiovascular disease
 - ☐ Myocardial infarction
 - ☐ Blood pressure change
 - ☐ Cardiovascular disease mortality
 - ☐ Other (specify)
-

Pregnancy and/or Lactating Outcomes

- ☐ Premature birth
 - ☐ Low birth weight/small for gestational age
 - ☐ Pre-eclampsia
 - ☐ Pregnancy hypertension
 - ☐ Infant mortality
 - ☐ Other (specify)
-

Adverse Events

- ☐ All-cause mortality
 - ☐ Cancer mortality
 - ☐ Renal outcomes
 - ☐ Soft tissue calcification
 - ☐ Other (specify)
-

Funding

- ☐ Government
 - ☐ Private foundation
 - ☐ Manufacturer
 - ☐ Other (specify)
 - ☐ Unclear
-

Have you reference mined this article?

- ☒ Yes (specify references needed to be checked)

☒ No

[Clear Response](#)

Has this form been checked by a second reviewer?

☒ Yes

☒ No [Clear Response](#)

Comments

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QUALITY of INTERVENTIONAL STUDIES

Instructions: Y=Yes; N=No; ND=No Data; NA=not applicable

Study Design

- ☐ Parallel, RCT
- ☐ Cross-over, RCT
- ☐ Cluster, quasi-RCT
- ☐ Non-randomized, but controlled trial
- ☐ Before-and-after trial
- ☐ Other interventional design (please explain in detail)

[Clear Response](#)

Appropriate Randomization Technique

- ☐ Y
- ☐ N
- ☐ ND
- ☐ NA

[Clear Response](#)

Allocation Concealment

- ☐ Y
- ☐ N
- ☐ ND
- ☐ NA

[Clear Response](#)

Appropriate Washout Period

- ☐ Y
- ☐ N
- ☐ ND
- ☐ NA

[Clear Response](#)

Is the Dropout Rate <20%

- ☐ Y
- ☐ N
- ☐ ND

[Clear Response](#)

Blinded Outcome Assessment

- ☐ Y
- ☐ N
- ☐ ND

[Clear Response](#)

Intention to Treat Analysis

- ☐ Y
- ☐ N
- ☐ ND
- ☐ NA

[Clear Response](#)

Appropriate Statistical Analysis

- ☐ Y
- ☐ N

☐ ND

[Clear Response](#)

Assessment for Confounding

☐ Y

☐ N

☐ ND

☐ NA

[Clear Response](#)

Clear Reporting with No Discrepancies

☐ Y

☐ N

[Clear Response](#)

OVERALL Grade

☐ A

☐ B (explanation for overall quality grade)

☐ C (explanation for overall quality grade)

[Clear Response](#)

Comments

QUALITY of COHORT OR NESTED CASE-CONTROL STUDIES

Population

a) Eligibility criteria clear?

☒ Y

☒ N

[Clear Response](#)

b) Sampling of population random or consecutive?

☒ Y

☒ N

[Clear Response](#)

Exposure (All)

a) Exposure assessor blinded to outcome info?

☒ Y

☒ N

[Clear Response](#)

b) Outcome assessor blinded to exposure measurement?

☒ Y

☒ N

[Clear Response](#)

Dietary assessment*

*Check “NA” and skip all questions if study did not use dietary assessment or biomarkers

a) Method reported?

- ☐ Y
- ☐ N
- ☐ NA

[Clear Response](#)

b) Food composition database or suppl composition reported?

- ☐ Y
- ☐ N
- ☐ NA

[Clear Response](#)

c) Internal calibration of method perform (if FFQ)?

- ☐ Y
- ☐ N
- ☐ NA

[Clear Response](#)

Biomarkers*

***Check “NA” and skip all questions if study did not use dietary assessment or biomarkers**

a) One of the prespecified methods* was used?

***Prespecified methods: HPLC, RIA kits, LC-MS/MS; EIA/Chemiluminescence**

- ☐ Y
- ☐ N
- ☐ NA

[Clear Response](#)

b) Time from sample collection to sample analysis reported?

- ☐ Y
- ☐ N
- ☐ NA

[Clear Response](#)

Comparator

a) Level of the exposure in comparative categories (e.g., quartiles) is given (ranges)?*

*applicable for categorical analyses only

- ☐ Y
- ☐ N

[Clear Response](#)

Statistical Analysis

a) Adjusted or matched for ANY confounders (other than age and sex)?*

*We will judge in the end if the set of confounders is adequate

- ☐ Y
- ☐ N

[Clear Response](#)

b) Justification of final adjusted model selection?

- ☐ Y
- ☐ N

[Clear Response](#)

Outcome

a) Clear definition of outcome, including time of ascertainment?

☐ Y

☐ N

[Clear Response](#)

b) Loss to follow-up <20%?

☐ Y

☐ N

[Clear Response](#)

c) Do the authors specify a primary outcome?

☐ Y

☐ N

☐ NA

[Clear Response](#)

Design

a) Prospective collection of data?

☐ Y

☐ N

[Clear Response](#)

b) Analysis was planned when cohort was formed?

☐ Y

☐ N

[Clear Response](#)

c) Justification of sample size (includes sample size calculations)?

☐ Y

- N
- NA

[Clear Response](#)

OVERALL Grade (A/B/C):

- A
- B (explanation for overall quality grade)
- C (explanation for overall quality grade)

[Clear Response](#)

Comments

Appendix F. Excluded Studies

Excluded Studies (From the Original Report)

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 lactoovo vegetarians and omnivores. <i>American Journal of Clinical Nutrition</i> 48 (1):131-8, 1988.	No outcomes of interest
Abbasi AA, Chemplavil JK, Farah S, Muller BF, Arnstein AR. Hypercalcemia in active pulmonary tuberculosis. <i>Annals of Internal Medicine</i> 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. <i>Journal of Pediatrics</i> 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. <i>Annals of Internal Medicine</i> 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. <i>Annals of Tropical Paediatrics</i> 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. <i>Archives of Disease in Childhood</i> 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. <i>Journal of Pediatric Gastroenterology & Nutrition</i> 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. <i>Nutrition & Cancer</i> 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. <i>European Journal of Cancer Prevention</i> 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. <i>European Journal of Clinical Nutrition</i> 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. <i>Clinical Chemistry</i> 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. <i>American Journal of Clinical Nutrition</i> 84 (3):602-9, 2006.	No outcomes of interest
Anonymous. Calcium supplementation during pregnancy reduces the risk of developing preeclampsia in nulliparous women. <i>Canadian Family Physician</i> 45:614, 618-20, 1999.	Editorial-like brief review
Anonymous. Vitamin D supplementation for northern native communities. <i>Indian and Inuit Health Committee, Canadian Paediatric Society. CMAJ Canadian Medical Association Journal</i> 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. <i>British Journal of Cancer</i> 71 (1):186-90, 1995.	No outcomes of interest
Armstrong AL, Osborne J, Coupland CA, Macpherson MB, Bassey EJ, Wallace WA. Effects of hormone replacement therapy on muscle performance and balance in post-menopausal women. <i>Clinical Science</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>American Journal of Obstetrics & Gynecology</i> . 191(5):1666-72, 2004 Nov.	>=20% subjects with diseases

Excluded Study	Reason
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
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

Excluded Study	Reason
Berube S, Diorio C, Masse B et al. Vitamin D and calcium intakes from food or supplements and mammographic breast density. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Lipids</i> 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. <i>American Journal of Hypertension</i> 1(3 Pt 3):149S - 152S, 1988.	In systematic review
Bischoff HA, Stahelin HB, Dick W et al. Effects of Vitamin D and calcium supplementation on falls: a randomized controlled trial.. <i>Journal of Bone & Mineral Research</i> 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? <i>Osteoporosis International</i> 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. <i>Archives of Internal Medicine</i> 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. <i>JAMA</i> 237 (3):262 -3, 1977.	No 25(OH)D or dietary Ca
Bogges 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. <i>Obstetrics & Gynecology</i> 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. <i>European Cancer Prevention Organisation Study Group. Lancet</i> 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. <i>Diseases of the Colon & Rectum</i> 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. <i>American Journal of Epidemiology</i> 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. <i>Archives of Family Medicine</i> 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.. <i>Journal of the National Cancer Institute</i> 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. <i>Journal of the National Cancer Institute</i> . 85(2):132-41, 1993 Jan 20.	No outcomes of interest
Boutron MC, Faivre J, Marteau P, Couillaud C, Senesse P, Quipourt V. Calcium, phosphorus, Vitamin D, dairy products and colorectal carcinogenesis: a French case--control study.. <i>British Journal of Cancer</i> 74 (1):145-51, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
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. <i>International Journal of Obesity</i> 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. <i>Southern Medical Journal</i> 100 (11):1061-2, 2007.	Review paper
Brekke HK, Ludvigsson J. Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study. <i>Pediatric Diabetes</i> 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. <i>Journal of the American Geriatrics Society</i> 2007; 55(2):234-239.	In Ottawa EPC report

Excluded Study	Reason
Brooke OG, Butters F, Wood C. Intrauterine Vitamin D nutrition and postnatal growth in Asian infants. <i>British Medical Journal Clinical Research Ed</i> 283 (6298):1024, 1981.	No 25(OH)D or dietary Ca
Brooke OG. Supplementary Vitamin D in infancy and childhood. <i>Archives of Disease in Childhood</i> 1983; 58(8):573-574.	Review paper
Brunvand L, Quigstad E, Urdal P, Haug E. Vitamin D deficiency and fetal growth. <i>Early Human Development</i> 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. <i>Acta Obstetrica et Gynecologica Scandinavica</i> 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. <i>Nutrition & Cancer</i> 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. <i>Journal of Endocrinology</i> 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. <i>Brazilian Journal of Medical & Biological Research</i> 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. <i>Journal of Reproductive Medicine</i> 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. <i>American Journal of Epidemiology</i> 142 (9):935-45, 1995.	Meta-analysis
Carlson GC, Howland WS, Goldiner PL, Kahn RC, Bertoni G, Turnbull AD. Adverse effects of calcium administration. Report of two cases. <i>Archives of Surgery</i> 113 (7):882-5, 1978.	Case report
Carlson LA, Derblom H, Lanner A. Effect of different doses of Vitamin D on serum cholesterol and triglyceride levels in healthy men. <i>Atherosclerosis</i> 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. <i>Journal of General Internal Medicine</i> 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. <i>Journal of the National Cancer Institute</i> 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. <i>American Journal of Nephrology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Pediatrics</i> 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). <i>Cancer Causes & Control</i> 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. <i>British Journal of Cancer</i> 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. <i>International Journal of Cancer</i> 60 (5):616-21, 1995.	No outcomes of interest
Cleghorn GJ, Tudehope DI. Neonatal intestinal obstruction associated with oral calcium supplementation. <i>Australian Paediatric Journal</i> 17(4):298-9, 1981.	Case report

Excluded Study	Reason
Cockburn F, Belton NR, Purvis RJ et al. Maternal Vitamin D intake and mineral metabolism in mothers and their newborn infants. <i>British Medical Journal</i> 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. <i>American Journal of Obstetrics & Gynecology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Biological Trace Element Research</i> 121 (3):193 -204, 2008.	>=20% subjects with diseases
Cong K, Chi S, Liu G. Calcium supplementation during pregnancy for reducing pregnancy induced hypertension. <i>Chinese Medical Journal</i> 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? <i>Age & Ageing</i> 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. <i>Journal of Bone & Mineral Research</i> 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. <i>Annals of the Rheumatic Diseases</i> 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. <i>Australian & New Zealand Journal of Obstetrics & Gynaecology</i> 39 (1):12-8, 1999.	In Hofmeyer 2007 systematic review
Dahifar H, Faraji A, Yassobi S, Ghorbani A. Asymptomatic rickets in adolescent girls. <i>Indian Journal of Pediatrics</i> 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. <i>Human Nutrition - Clinical Nutrition</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Clinical Science</i> 70 (3):285-93, 1986.	No outcomes of interest
Davies KM, Heaney RP, Recker RR et al. Calcium intake and body weight. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>Journal of Human Nutrition & Dietetics</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Lancet</i> 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. <i>American Journal of Clinical Nutrition</i> 76 (4):845-51, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Devereux G, Litonjua AA, Turner SW et al. Maternal Vitamin D intake during pregnancy and early childhood wheezing. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Pediatric Gastroenterology & Nutrition</i> 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. <i>Journal of Bone & Mineral Research</i> 17(5):891-7, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
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 between 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, Stithantrakul 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 Obstetrica 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
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, Couillaud 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

Excluded Study	Reason
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. <i>Hypertension</i> 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. <i>Revista Espanola de Enfermedades Digestivas</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Diabetes Care</i> 26 (12):3237 -42, 2003.	Observational study estimated Vitamin D supplement doses
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. <i>Journal of Human Hypertension</i> 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 <i>J Clin Endocrinol Metab</i> 1997 Dec;82(12):4074]. <i>Journal of Clinical Endocrinology & Metabolism</i> 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 <i>Int J Epidemiol.</i> 2006 Apr;35(2):217-20; PMID: 16303809]. <i>International Journal of Epidemiology</i> 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. <i>American Journal of Preventive Medicine</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 15 (2):364-72, 2006.	Pooled analysis
Gertner JM, Domenech M. 25-HydroxyVitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. <i>Journal of Clinical Pathology</i> 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. <i>Biology of the Neonate</i> 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. <i>JAMA</i> 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. <i>Circulation</i> 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.. <i>Journal of the National Cancer Institute</i> 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. <i>Cancer Research</i> 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.. <i>Annals of Internal Medicine</i> 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. <i>Journal of the American Dietetic Association</i> 106 (7):1066-73 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
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. <i>British Journal of Nutrition</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>Anticancer Research</i> 26 (4A):2605-14, 2006.	Ecological study

Excluded Study	Reason
Grau MV, Baron JA, Barry EL et al. Interaction of calcium supplementation and nonsteroidal anti-inflammatory drugs and the risk of colorectal adenomas. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 14(10):2353-8, 2005.	In Weigarten 2008 systematic review
Greene MF. Trial of calcium to prevent preeclampsia. <i>Journal of Women's Health</i> 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. <i>Journal of Pediatrics</i> 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. <i>Journal of Pediatrics</i> 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. <i>Journal of Pediatrics</i> 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. <i>Journal of Pediatrics</i> 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. <i>Endocrinologia Experimentalis</i> . 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. <i>American Journal of Clinical Nutrition</i> 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. <i>International Journal of Obesity</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>European Journal of Clinical Nutrition</i> 43 (6):421-30, 1989.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
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. <i>Journal of Steroid Biochemistry & Molecular Biology</i> 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. <i>Hypertension</i> 17(1 Suppl):1150-4, 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. <i>Journal of the American Medical Directors Association</i> 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? <i>Journal of Bone & Mineral Research</i> 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. <i>Nutrition Journal</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Lancet</i> 1985; 1(8434):925.	Superseded 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. <i>Obstetrics & Gynecology</i> 91 (4):585 -90, 1998.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Herrmann U, Schuille 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. <i>Biomedicine & Pharmacotherapy</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>Australian & New Zealand Journal of Obstetrics & Gynaecology</i> 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. <i>Journal of Pediatrics</i> 1975; 86(6):928-935.	No clear Vitamin D dose for term infants
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. <i>Journal of Pediatrics</i> 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. <i>European Journal of Clinical Nutrition</i> 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. <i>Hypertension in Pregnancy</i> 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. <i>Digestion</i> 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. <i>European Journal of Cancer Prevention</i> 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. <i>Am J Clin Nutr</i> 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 <i>Obesity</i> (Silver Spring). 2007 Oct;15(10):2520]. <i>Obesity</i> 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. <i>JAMA</i> 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. <i>Cancer</i> 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. <i>Nutrition & Cancer</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>American Journal of Nephrology</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 7 (4):291-5, 1998.	Multiple antioxidant trials analyses
Hypponen E, Hartikainen AL, Sovio U, Jarvelin MR, Pouta A. Does Vitamin D supplementation in infancy reduce the risk of pre-eclampsia? <i>European Journal of Clinical Nutrition</i> 2007; 61(9):1136-1139.	Observational study estimated Vitamin D supplement doses

Excluded Study	Reason
Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of Vitamin D and risk of type 1 diabetes: a birth-cohort study. <i>Lancet</i> 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. <i>Annals of the New York Academy of Sciences</i> 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 <i>Am J Clin Nutr</i> 1999 Mar;69(3):577]. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>International Journal of Gynaecology & Obstetrics</i> 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. <i>Current Osteoporosis Reports</i> 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. <i>Annals of Epidemiology</i> 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 <i>N Engl J Med</i> . 2006 Mar 9;354(10):1102]. <i>New England Journal of Medicine</i> 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. <i>South African Medical Journal Suid -Afrikaanse Tydskrif Vir Geneeskunde</i> 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. <i>Journal of Steroid Biochemistry & Molecular Biology</i> 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. <i>American Journal of Clinical Nutrition</i> 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.. <i>American Journal of Obstetrics & Gynecology</i> 179 (4):1032-7, 1998.	No 25(OH)D or dietary Ca
John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. <i>Journal of Steroid Biochemistry & Molecular Biology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Nutrition for the Elderly</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Clinical Densitometry</i> 2(2):109-15, 1999.	No outcomes of interest
Jorde R, Bonna KH. Calcium from dairy products, Vitamin D intake, and blood pressure: the Tromso Study.. <i>American Journal of Clinical Nutrition</i> 71 (6):1530-5, 2000.	No outcomes of interest
Kampman E, Giovannucci E, van 't V et al. Calcium, Vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. <i>Am J Epidemiol</i> 1994; 139(1):16-29.	Same cohorts as Wu 2002 RefID 529 (HPFS & NHS) and same exposure-outcome relationship but shorter follow-up

Excluded Study	Reason
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
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. <i>Journal of Clinical Investigation</i> 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. <i>Bone</i> 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.. <i>Journal of the American Dietetic Association</i> 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. <i>American Journal of Clinical Nutrition</i> 86 (3):714-7, 2007.	No outcomes of interest
Lakdawala DR, Widdowson EM. Vitamin-D in human milk. <i>Lancet</i> 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. <i>Human Nutrition - Clinical Nutrition</i> 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. <i>Journal of Nutrition, Health & Aging</i> 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. <i>Journal of the American College of Nutrition</i> 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. <i>Public Health Nutrition</i> 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. <i>Menopause</i> 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). <i>Journal of the American Geriatrics Society</i> 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. <i>Endocrinologia Experimentalis</i> . 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. <i>Journal of Toxicology - Clinical Toxicology</i> 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.. <i>American Journal of Clinical Nutrition</i> 60 (5):744 -50, 1994.	In Winzenberg 2007 systematic review, no outcomes of interest
Levine AJ, Harper JM, Ervin CM et al. Serum 25-hydroxyVitamin D, dietary calcium intake, and distal colorectal adenoma risk. <i>Nutrition & Cancer</i> 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. <i>Controlled Clinical Trials</i> 17(5):442-69, 1996.	Methods for trial
Levine RJ, Hauth JC, Curet LB et al. Trial of calcium to prevent preeclampsia.. <i>New England Journal of Medicine</i> 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. <i>Journal of Renal Nutrition</i> 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. <i>Hypertension</i> 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. <i>Journal of the American Dietetic Association</i> 2007; 107(9):1541-1551.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
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. <i>Journal of the American College of Nutrition</i> . 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. <i>Acta Medica Scandinavica</i> 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. <i>Cancer Research</i> 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. <i>New England Journal of Medicine</i> 313 (22):1381-4, 1985.	No outcomes of interest
Liu LS. Epidemiology of hypertension and cardiovascular disease--China experience. <i>Clinical & Experimental Hypertension - Part A, Theory & Practice</i> 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. <i>Diabetes Care</i> 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. <i>Acta Medica Scandinavica</i> 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, actiVitamins, and calcium intake on bone mineral density in children. <i>Clinical Pediatrics</i> 35 (4):185-9, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lopez-Jaramillo P, Delgado F, Jacome P, Teran E, Ruano C, Rivera J. Calcium supplementation and the risk of preeclampsia in Ecuadorian pregnant teenagers. <i>Obstetrics & Gynecology</i> 90 (2):162-7, 1997.	In Hofmeyer 2007 systematic review
Lopez-Jaramillo P, Narvaez M, Weigel RM, Yopez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. <i>British Journal of Obstetrics & Gynaecology</i> 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. <i>Clinical Pharmacology & Therapeutics</i> 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. <i>Journal of Nutrition</i> 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. <i>Netherlands Journal of Medicine</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity</i> 27 (6):669-76, 2003.	No outcomes of interest
Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. <i>American Journal of Hypertension</i> 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. <i>Nutrition & Cancer</i> 32 (3):146 -53, 1998.	Superseded by Pietinen 1999

Excluded Study	Reason
Mandic-Puljek M, Mandic ML, Perl A, Kenjeric D. Calcium intake, food sources and seasonal variations in eastern Croatia. <i>Collegium Antropologicum</i> 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. <i>Maturitas</i> 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. <i>Clinical Science</i> 91 (3):313-8, 1996.	No UL outcomes: saturation of CaOx
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. <i>Acta Paediatrica Scandinavica</i> 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. <i>Acta Paediatrica Scandinavica</i> 72 (6):817-21, 1983.	Not RCT arrow 4 study
Markestad T. Plasma concentrations of Vitamin D metabolites in unsupplemented breast-fed infants. <i>European Journal of Pediatrics</i> 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. <i>International Journal of Epidemiology</i> 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. <i>Journal of the National Cancer Institute</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 51 (5):1138 -42, 1980.	Case report
Masse PG, Tranchant CC, Jougoux 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. <i>Journal of Human Nutrition & Dietetics</i> 21(2):117-28, 2008.	No outcomes of interest
Matheson NA. Letter: Multiple sclerosis and diet. <i>Lancet</i> 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. <i>Journal of Steroid Biochemistry & Molecular Biology</i> 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. <i>Mineral & Electrolyte Metabolism</i> 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. <i>Calcified Tissue International</i> 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. <i>Calcified Tissue International</i> 33 (4):365-8, 1981.	No 25(OH)D or dietary Ca
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. <i>Annals of Internal Medicine</i> 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.. <i>Arthritis & Rheumatism</i> 50(1):72-7, 2004.	Observational study estimated Vitamin D supplement doses
Methy N, Biquet C, Boutron-Ruault MC, Paillot B, Faivre J, Bonithon-Kopp C. Dietary fatty acids and recurrence of colorectal adenomas in a European intervention trial. <i>Nutrition & Cancer</i> 60 (5):560-7, 2008.	no 25(OH)D or dietary Ca

Excluded Study	Reason
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. <i>American Journal of Epidemiology</i> 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. <i>Acta Paediatrica Scandinavica</i> 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). <i>Annals of Epidemiology</i> 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. <i>Diabetologia</i> 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. <i>European Journal of Clinical Nutrition</i> 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. <i>International Journal of Epidemiology</i> 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. <i>Journal of Nephrology</i> 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. <i>American Journal of Hypertension</i> 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. <i>JAMA</i> . 296(23):2832-8, 2006 Dec 20.	No outcomes of interest
Murray S, Marco MP, Craver L, Rue M, Valdivielso JM, Fernandez E. Influence of mineral metabolism parameters on pulse pressure in healthy subjects.. <i>Clinical Nephrology</i> 2006; 66(6):411-417.	No 25(OH)D or dietary Ca
Nakamura K, Nishiwaki T, Ueno K, Yamamoto M. Age-related decrease in serum 25-hydroxyVitamin D concentrations in the frail elderly: a longitudinal study. <i>Journal of Bone & Mineral Metabolism</i> 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. <i>Japanese Journal of Medicine</i> 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. <i>Pediatrics</i> 1993; 92(6):862-864.	Case report
Narang NK, Gupta RC, Jain MK. Role of Vitamin D in pulmonary tuberculosis. <i>Journal of the Association of Physicians of India</i> 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. <i>Pediatric Nephrology</i> 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. <i>Clinical Endocrinology</i> 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. <i>Osteoporosis International</i> 1919;673-9.	not RCT bone study (postmenopausal women)
Nilas L, Christiansen C. Treatment with Vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. <i>International Journal of Obesity</i> 8(5):407-11, 1984.	Review paper
Niromanesh S, Laghai S, Mosavi-Jarrahi A. Supplementary calcium in prevention of pre-eclampsia. <i>International Journal of Gynaecology & Obstetrics</i> 74 (1):17-21, 2001.	In Hofmeyer 2007 systematic review

Excluded Study	Reason
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
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, Winkhofer-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, Hulse 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
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

Excluded Study	Reason
Pittas AG, Harris SS, Stark PC, Wason-Hughes B. The effects of calcium and Vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. <i>Diabetes Care</i> 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? <i>Lung Cancer</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>Epidemiology</i> 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. <i>Journal of Obstetrics & Gynaecology Research</i> 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. <i>British Journal of Nutrition</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Maternal & Child Nutrition</i> 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. <i>American Journal of Obstetrics & Gynecology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>American Journal of Hypertension</i> 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. <i>European Journal of Clinical Nutrition</i> 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. <i>American Journal of Hypertension</i> 4(11):642S-645S, 1991.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Roberts CC, Chan GM, Folland D, Rayburn C, Jackson R. Adequate bone mineralization in breast-fed infants. <i>Journal of Pediatrics</i> 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. <i>Cancer Causes & Control</i> 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. <i>Hypertension in Pregnancy</i> 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 <i>Garcinia atroviridis</i> on the short term treatment of obese women in Thailand. <i>Asia Pacific Journal of Clinical Nutrition</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Journal of Pediatrics</i> 101 (4):500-3, 1982.	In Ottawa EPC report

Excluded Study	Reason
Rourke KM, Brehm BJ, Cassell C, Sethuraman G. Effect of weight change on bone mass in female adolescents. <i>Journal of the American Dietetic Association</i> 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. <i>Gut</i> 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. <i>Cancer</i> 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. <i>Hypertension in Pregnancy</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Maternal & Child Nutrition</i> 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. <i>Hypertension</i> 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. <i>Annals of Epidemiology</i> 5(2):108-18, 1995.	No outcomes of interest
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. <i>Hypertension</i> 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. <i>Hypertension</i> 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. <i>Journal of Urology</i> 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. <i>Journal of Urology</i> 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. <i>International Journal of Gynecological Cancer</i> 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. <i>Obesity</i> 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. <i>Obstetrics & Gynecology</i> 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. <i>Obstetrics & Gynecology</i> 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. <i>Journal of Human Nutrition</i> 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. <i>Endocrine Journal</i> 41 (4):329-37, 1994.	Case report

Excluded Study	Reason
Satterfield S, Cutler JA, Langford HG et al. Trials of hypertension prevention. Phase I design. <i>Annals of Epidemiology</i> 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]. <i>American Journal of Clinical Nutrition</i> 83 (4):754 -9, 2006.	>=20% subjects with diseases
Schumann SA, Ewigman B. Double-dose Vitamin D lowers cancer risk in women over 55. <i>Journal of Family Practice</i> 2007; 56(11):907-910.	Editorial-like brief review
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). <i>Cancer Causes & Control</i> 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? <i>Diabetes Care</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Clinical Science</i> 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. <i>American Journal of Obstetrics & Gynecology</i> 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. <i>Anticancer Research</i> 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. <i>Journal of the American Geriatrics Society</i> 52 (9):1543-8, 2004.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Sita-Lumsden A, Laphorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and Vitamin D deficiency: the contribution of diet and exposure to sunlight. <i>Thorax</i> 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. <i>Physics in Medicine & Biology</i> 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.. <i>Journal of the American Dietetic Association</i> 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 activity. <i>Journal of Pediatrics</i> 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. <i>Pediatrics</i> 99(6): E12, 1997.	No independent Ca effect
Specker BL, Tsang RC, Ho M, Miller D. Effect of vegetarian diet on serum 1,25-dihydroxyVitamin D concentrations during lactation. <i>Obstetrics & Gynecology</i> 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. <i>Journal of Pediatrics</i> 107 (3):372-6, 1985.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. <i>Hypertension</i> 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. <i>Surgery</i> 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. <i>Diabetic Medicine</i> 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. <i>Clinical Rehabilitation</i> 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. <i>Journal of Nutrition</i> 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.. <i>Journal of the American Board of Family Practice</i> 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. <i>Journal of the American Society of Nephrology</i> 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. <i>Obesity</i> 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. <i>Prostate</i> 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. <i>Obesity Research</i> 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 <i>Med J Aust.</i> 2005 Jan 3;182(1):48 Note: Thompson, Katherine [corrected to Thomson, Katherine]]. <i>Medical Journal of Australia</i> 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. <i>Journal of Obstetrics & Gynaecology</i> 21(3):281-8, 1995.	No outcomes of interest
Tretli S, Hernes E, Berg JP, Hestvik UE, Rødsahl TE. Association between serum 25(OH)D and death from prostate cancer. <i>British Journal of Cancer</i> 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. <i>Journal of Pediatrics</i> 86 (6):936-41, 1975.	No 25(OH)D or dietary Ca
Twoogor 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>International Journal of Epidemiology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>American Journal of Clinical Nutrition</i> 82 (3):700-6, 2005.	No 25(OH)D or dietary Ca

Excluded Study	Reason
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. <i>American Journal of Clinical Nutrition</i> 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.. <i>Aging-Clinical & Experimental Research</i> 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. <i>Journal of the American Geriatrics Society</i> 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. <i>Journal of the American Geriatrics Society</i> 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. <i>American Journal of Obstetrics & Gynecology</i> . 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. <i>Obstetrical & Gynecological Survey</i> 53 (9):575-85, 1998 Sep.	Not relevant systematic review
Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. <i>American Journal of Obstetrics & Gynecology</i> 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. <i>Journal of Clinical Endocrinology & Metabolism</i> 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. <i>BMC Public Health</i> 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]. <i>Journal of the National Cancer Institute</i> 96 (12):921-5, 2004.	In Weigarten 2008 SR
Wallace K, Baron JA, Karagas MR et al. The association of physical activity and body mass index with the risk of large bowel polyps. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Journal of Nursing Scholarship</i> 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. <i>Journal of the Association of Physicians of India</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Gastroenterology</i> 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. <i>American Journal of Clinical Nutrition</i> 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. <i>Maturitas</i> . 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. <i>Journal of the National Cancer Institute</i> 97 (22):1688-94, 2005.	No 25(OH)D or dietary Ca
Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. <i>American Journal of Hypertension</i> 6 (9):799-805, 1993.	In systematic review

Excluded Study	Reason
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.	Superseded 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 activity and dairy consumption: Calcium Weighs-In. Journal of Physical Activity & 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
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

Excluded Studies (From the Current Report)

Rejected for Study Design—N=191

1. Abrams SA. Calcium and vitamin D requirements for optimal bone mass during adolescence. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2011 Nov;14(6):605-9. PMID: 21849894.
2. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. *Osteoporosis International*. 2009 Feb;20(2):239-44. PMID: 18551242.
3. Adams SV, Newcomb PA, Burnett-Hartman AN, et al. Circulating 25-hydroxyvitamin-D and risk of colorectal adenomas and hyperplastic polyps. *Nutrition & Cancer*. 2011;63(3):319-26. PMID: 21432725.
4. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. *Carcinogenesis*. 2009 May;30(5):769-76. PMID: 19255064.
5. Allan K, Devereux G. Diet and asthma: nutrition implications from prevention to treatment. *Journal of the American Dietetic Association*. 2011 Feb;111(2):258-68. PMID: 21272700.
6. Alvarez JA, Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. *International Journal of Endocrinology Print*. 2010;2010:351385. PMID: 20011094.
7. Alzaim M, Wood RJ. Vitamin D and gestational diabetes mellitus. *Nutrition Reviews*. 2013 Mar;71(3):158-67. PMID: 23452283.
8. Annweiler C, Rolland Y, Schott AM, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. *Journals of Gerontology Series A-Biological Sciences & Medical Sciences*. 2012 Nov;67(11):1205-11. PMID: 22503994.
9. Annweiler C, Schott A-M, Montero-Odasso M, et al. Cross-sectional association between serum vitamin D concentration and walking speed measured at usual and fast pace among older women: the EPIDOS study. *Journal of Bone & Mineral Research*. 2010 Aug;25(8):1858-66. PMID: 20205167.
10. Assimos D. Re: Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. *Journal of Urology*. 2011 Nov;186(5):1918. PMID: 21993105.
11. Attar SM. Vitamin D deficiency in rheumatoid arthritis. Prevalence and association with disease activity in Western Saudi Arabia. *Saudi Medical Journal*. 2012 May;33(5):520-5. PMID: 22588813.
12. Barake R, Weiler H, Payette H, et al. Vitamin D supplement consumption is required to achieve a minimal target 25-hydroxyvitamin D concentration of > or = 75 nmol/L in older people. *Journal of Nutrition*. 2010 Mar;140(3):551-6. PMID: 20089782.

13. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *Journal of Bone & Mineral Research*. 2009 May;24(5):935-42. PMID: 19113911.
14. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, et al. Benefit-risk assessment of vitamin D supplementation. *Osteoporosis International*. 2010 Jul;21(7):1121-32. PMID: 19957164.
15. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040. PMID: 21505219.
16. Boyce AM, Gafni RI. Approach to the child with fractures. *Journal of Clinical Endocrinology & Metabolism*. 2011 Jul;96(7):1943-52. PMID: 21734001.
17. Chaganti RK, Parimi N, Cawthon P, et al. Association of 25-hydroxyvitamin D with prevalent osteoarthritis of the hip in elderly men: the osteoporotic fractures in men study. *Arthritis & Rheumatism*. 2010 Feb;62(2):511-4. PMID: 20112402.
18. Chai W, Maskarinec G, Cooney RV. Serum 25-hydroxyvitamin D levels and mammographic density among premenopausal women in a multiethnic population. *European Journal of Clinical Nutrition*. 2010 Jun;64(6):652-4. PMID: 20216557.
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No Outcomes of Interest—N=306

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Appendix G. Serum Vitamin D Assay Reporting in Randomized Controlled Trials (RCTs)

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard ^a
Studies in Original Report					
Bjorkman, 2008 ²⁶³	Serum 25(OH)D	HPLC ³⁰⁷	Finland/ assay dates not reported	Limit of quantification: 10 nmol/L. Intra-assay coefficient of variation: 5.6% (21.6 nmol/l; n=14) and 3.7% at 138nmol/l (n=15). Total CV: 7.3% at 16.4nmol/l (n=12) and 5.7% at 167nmol/l(n=15)	Not Reported (NR)
Blum, 2008 ²⁷⁹	Serum 25(OH)D	Competitive protein binding assay	US/assay dates not reported	NR	NR
Bolton-Smith, 2007 ²⁷⁴	Serum 25(OH)D	Radioimmunoassay (RIA) (DiaSorin, Wokingham, UK)	UK/assay dates not reported	NR	NR
Bunout, 2006 ¹⁸³	Serum 25(OH)D	Not described	NR	NR	NR
Chan, 1982 ³⁰⁰	Serum 25(OH)D	Competitive protein binding assay ³⁰⁸	US/assay dates not reported	Coefficient of variation: 9%	NR
Chapuy, 1997 ²⁸⁰	Serum 25(OH)D	RIA (Incstar Corp, Stillwater, MN)	France/assay dates not reported	Intra-assay variance: 5% Inter-assay variance: 11%	NR
Chel, 2008 ²⁸¹	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Netherlands/assay dates not reported	Inter-assay coefficient of variation:10% at 30 nmol/L	NR
Dawson-Hughes, 1997 ²⁸⁹	Plasma 25(OH)D Plasma (1,25)D2	25(OH)D: Competitive protein binding assay ³⁰⁹ 1,25 di(OH)D: Competitive protein-binding method ³¹⁰	US/assay dates not reported	NR	NR
DeRoisy, 2002 ²⁸²	Serum 25(OH)D	RIA (Incstar, Stillwater, MN, USA).	Belgium/assay dates not reported	Intra-assay coefficient of variation: 8% Inter-assay coefficient of variation: < 12%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard ^a
El-Hajj-Fuleihan, 2006 ⁴⁸	Serum 25(OH)D Serum 1,25-dihydroxyvitamin D (1,25(OH)2D)	25(OH)D: competitive protein binding assay (DiaSorin, Incstar, Saluggia, Italy) 1,25(OH)2D: RIA (IDS Immuno-Diagnostic Systems, Boldon, UK).	NR	Intra- and interassay Coefficients of Variation <13% at a serum concentration of 47 ng/ml. Intra- and interassay coefficients of variation < 10% at serum concentrations between 10 and 100 pg/ml	NR
Harris, 2002 ²⁹⁰	Plasma 25(OH)D3 Plasma 25(OH)D	25(OH)D3: high performance liquid chromatography 25(OH)D: competitive protein binding assay	US/Assay dates not reported	NR	NR
Heaney, 2003 ²⁹¹	Serum 25(OH)D	RIA (Nichols Institute Diagnostics, San Juan Capistrano CA)	US/assay dates not reported	NR	NR
Heikkinen, 1998 ²⁹²	Serum 25OHD and 1,25(OH)2D	25OHD and 1,25(OH)2D : competitive protein binding assays using vitamin D binding proteins following purification on dual HPLC with UV detection ³¹¹	Finland/assay dates not reported but conducted at baseline and 1 year later	Interassay coefficient of variation (CV) was less than 8% in serum 25OHD analysis	NR
Himmelstein, 1990 ²⁸³	Serum 1,25(OH)2D 25OHD	1,25(OH)2D: calf thymus radioreceptor assay ³¹⁰ 25(OH)D: competitive protein binding assay ³⁰⁹	US/assay dates not reported	1,25(OH)2D Intra-assay coefficient of variation: 5% Inter-assay coefficient of variation: 11% 25(OH)D: Intra-assay coefficient of variation: 5% Inter-assay coefficient of variation: 10%	NR
Honkanen, 1990 ²⁹³	Serum 25(OH)D	25(OH)D: competitive protein binding assay ³¹¹	Finland/assay dates not reported	NR	NR
Jensen, 2002 ²⁹⁴	Serum 25(OH)D	Competitive protein-binding assay (Nichols Institute Diagnostics, San Juan Capistrano, CA)	US/assay dates not reported	NR	NR
Kenny, 2003 ²⁸⁴	Serum 25(OH)D	Competitive protein binding assay (Endocrine Sciences Inc., Calabasas Hills, CA)	US/assay dates not reported	Intra-assay coefficient of variation: <10%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard ^a
Krieg, 1999 ²⁸⁵	Serum 25(OH)D	Protein binding assay (Amersham Life Science, Little Chalfont, Bucks, UK)	Switzerland/assay dates not reported	NR	NR
Nelson, 2009 ²⁹⁵	Serum 25(OH)D	RIA	US/2005–2006	Intra-assay and inter-assay coefficients of variation <10%	NR
Orwoll, 1988 ²⁹⁶	Serum 25(OH)D 1,25(OH)2D 24,25(OH)2D	25(OH)D: Competitive protein binding assay ^{312,313} 1,25(OH)2D and 24,25(OH)2D determined by Anthony Norman ³¹⁴	US/assay dates not reported	NR	NR
Patel, 2001 ²⁹⁷	Serum 25(OH)D	RIA (INCSTAR)	UK/assay dates not reported	Sensitivity: 7.5nmol/l Intra-assay precision: 6.1% Inter-assay precision: 15.6%	NR
Pfeiffer, 2001 ²³⁸	Serum 25OHD3, and 1,25-(OH)2D3	RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA)	Germany/assay dates not reported	Coefficients of variation: 5.5–7.9%	NR
Pfeiffer, 2000 ²⁸⁶	Serum 25OHD3, and 1,25-(OH)2D3	RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA)	Germany/assay dates not reported	Coefficients of variation: 5.5–7.9%	NR
Riis, 1984 ²⁹⁸	Serum 25OHD3, 24, 25 (OH) ₂ D3, and 1,25-(OH) ₂ D3	25(OH)D: UV detection 1,25(OH)2D and 24,25(OH)2D determined by competitive protein binding assay ³¹⁵	Denmark/assay dates not reported	Intra-assay and inter-assay coefficients of variation: 1,25(OH)2D: 13% and 15% 24, 25(OH)2D: 14% and 17% 25(OH)D: 10% and 12%	NR
Trang, 1998 ²⁹⁹	Serum 25(OH)D 1,25(OH)2D	25(OH)D: RIA (INCSTAR, Stillwater MN) 1,25(OH)2D: calf thymus competitive protein binding assay	Canada/assay dates not reported	25(OH) D consistently within 1SD of the method group mean for the International External Quality Assessment Scheme	Results of the 25(OH)D assay method were consistently within 1 SD of the method group mean in the International External Quality Assessment Scheme proficiency survey for this metabolite
Sorva, 1991 ²⁸⁷	Serum 25(OH)D and 1,25-(OH)2D3	25(OH)D: competitive protein binding assay ³¹⁶ 1,25(OH)2D3: competitive protein binding assay ³¹⁰	Finland/assay dates not reported	NR	NR
Zhu, 2008 ²⁷⁵	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Australia/assay dates not reported	NR	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard ^a
Studies Identified for Current Report					
Gaanmaa, 2012 ²⁷⁸	Plasma 25(OH)D	CLIA TOTAL (LIAISON DiaSorin, Stillwater, MI, USA)	US/4/10–6/10	NR	NR
Gepner, 2012 ²²⁹	Serum 25(OH)D	HPLC ^{317,318}	US/assay dates not reported	NR	NR
Islam, 2010 ²⁶⁷	Serum (OH)D	RIA OCEIA (IDS, Boldon, UK)	Finland/assay dates not reported	Intra-and inter-assay coefficients of variation: 5.4 and 7.0 %	DEQAS
Jorde, 2010 ²³⁰	Total 25(OH)D	RIA (DiaSorin, Stillwater MN)	Norway / Assay dates not reported	Intra-assay and total coefficient of variation: 6% and 14%	NR
Karkainen, 2010 ²⁶⁹	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Finland/assay dates not reported	Coefficient of Variation: 8.2% to 11.0%	NR
Kukuljian, 2011 ²⁷²	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Australia/assay dates not reported	Coefficient of Variation: 3.9 – 5.8%	NR
Li-Ng, 2009 ¹⁵⁰	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	US/assay dates not reported	Intra-assay Variability: 4.1% Inter-assay Variability: 7.0%	DEQAS
MacDonald, 2013 ²⁴⁵	Serum 25(OH)D2 and 3	HPLC-tandem mass spectrometry	UK/assay dates not reported	Interassay coefficients of variation <10%	NIST standard used. Lab also participates in DEQAS
Molgaard, 2010 ²⁴⁸	Serum 25(OH)D	HPLC-based assay ³¹⁹	Denmark/assay dates not reported	Intra- and inter-assay coefficients of variability: 4.3% and 6.3%, respectively	DEQAS
Nieves, 2012 ²⁴⁴	Serum 25(OH)D and 1,25di(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	US/assay dates not reported	Coefficient of variation <12%	NR
Pfeifer, 2009 ¹⁸⁶	Serum 25(OH)D	RIA (Immunodiagnostic Systems, Boldon, UK)	Germany/assay dates not reported	NR	NR (validated against HPLC)
Salehpour, 2012 ²³⁴	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited).	Iran/assay dates not reported	Intra- and inter-assay coefficients of variation: 6.9 and 8.1 %, respectively	NR
Salovaara, 2010 ²⁶⁰	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Finland/assay dates not reported	Coefficient of variation: 8.2% to 11.0%	NR
Toxqui, 2013 ²²⁸	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited, UK).	Spain/assay dates not reported	Intra- and inter-assay coefficients of variation: 5.6%, 6.4%, respectively	NR
Wamberg, 2013 ²³⁶	Serum 25(OH)D2 and 3	HPLC tandem mass spec ³²⁰	Denmark/assay dates not reported	NR	NR
Witham, 2013 ²³⁵	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited, UK).	UK/assay dates not reported	NR	NR
Wood, 2012 ²³¹	Serum 25(OH)D2 and 3	HPLC tandem mass spec	UK/assay dates not reported	Coefficients of variation <10%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard ^a
Zhu, 2010 ¹⁸⁸	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Australia/assay dates not reported	NR	NR

Legend:

^aThe reference standard refers to a sample whose concentration of 25(OH)D has been ascertained by a recognized entity, such as the United States National Institute of Standards and Technology (NIST), that is used to establish the reliability of an assay.

CLIA=chemiluminescence immunoassay CV=Coefficient of Variation; 25(OH)D=25-hydroxyvitamin D; 1,25(OH)₂D=1,25-Dihydroxyvitamin D; 1,25 di(OH)D=1,25-dihydroxyvitamin D; 24,25(OH)₂=Dihydroxyvitamin D; HPLC= High Performance Liquid Chromatography; nmol=nanomoles; NR=Not Reported; RCT=Randomized Controlled Trial(s); RIA=radioimmunoassay; UV=Ultraviolet

Appendix H. Studies Reporting Key Outcomes Stratified by Vitamin D Assay Method

Tables 4, 5: Growth (vitamin D)

Tables 6, 7: Birth weight (vitamin D)

Tables 14–17: Total cancer/cancer mortality (vitamin D)

Tables 18, 19: Prostate cancer (vitamin D)

Tables 26, 27: Breast cancer (vitamin D)

Tables 28, 29: Pancreatic cancer (vitamin D)

Tables 30c and d, 31c and d: Infectious illnesses (vitamin D)

Tables 32a, 33a: Preeclampsia (vitamin D)

Tables 35d, 36d: Fracture (vitamin D)

Tables 38, 39: All-cause mortality (vitamin D)

Tables 42, 43: Blood pressure (vitamin D)

Tables 44, 45: Bone mineral density (vitamin D)

Tables 65, 66: Bone mineral density (vitamin D+calcium)

List of Acronyms and Abbreviations Included in Tables

Abbreviation	Term	Abbreviation	Term
ACS	Aortic calcification score	MONICA	Multinational MONItoring of trends and determinants in Cardiovascular disease Study
ADL	Activities of Daily Living	MI	Myocardial infarction
ASA	Acetyl salicylic acid (aspirin)	n	Number
ATBC	Alpha Tocopherol, Beta Carotene Cancer Prevention Study	na	Not applicable
BMC	Bone mineral content	nd	No data
BMD	Bone mineral density	NHS	Nurses Health Study
BMI	Body mass index	nr	Not reported
BP	Blood pressure	NSAIDS	Non-steroidal Antiinflammatories
Ca	Calcium	NHANES	National Health and Nutrition Examination Survey
CHS	Cardiovascular Health Study		
CKD	Chronic kidney disease		nanomoles
CPS	Cancer Prevention Study	nmol	
CRC	Colorectal cancer	OR	Odds ratio
CRP	C-reactive protein		
CVD	Cardiovascular disease	PASE	Physical Activity Score For The Elderly
d	Day	PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
DBP	Diastolic blood pressure	PTH	Parathyroid hormone
DM	Diabetes mellitus	Q	Quartile
Dx	Diagnosis	RCT	Randomized controlled trial
eGFR	Estimated glomerular filtration rate	RIA	radioimmunoassay;
EPIC	European Prospective Investigation into Cancer and Nutrition	RR	Relative risk
ESTHER	EStrogen and THromboEmbolism Risk Study	SC	Size-corrected
GFR	Glomerular filtration rate	SD	Standard deviation
HDL	High-density lipoprotein	SBP	Systolic blood pressure
HLA	Human leukocyte antigen		
HPFS	Health Professionals Follow-Up Study	SES	Socioeconomic status
HPLC	high performance liquid chromatography	SPPB	Secondary-Short Physical Performance Battery
HR	Hazard ratio	TUAG	Timed Up and Go
HTN	Hypertension	UK	United Kingdom
InChianti	Invecchiare nel Chianti	UV	Ultraviolet
INTAPP	International Trial of Antioxidants in the Prevention of Pre-eclampsia	Vit	Vitamin
IQR	Interquartile range	VTE	Venous thromboembolism
IU	International Units	WHI	Women's Health Initiative
KORA	Cooperative Health Research in the Region Augsburg	Wk	Week
LDL	Low-density lipoprotein	Y, y	year
MEC	Mobile Examination Center	YRS	Years
MESA	Multi-ethnic Study of Atherosclerosis		
MI	Myocardial infarction		

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor assay						
Maxwell 1981 ⁵¹ Brooke 1980 ⁴⁷ UK (51°N) [6793058] [6989438]	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	<p>pregnancy</p> <p>nd</p> <p>0</p>	25(OH)D at 28-32 wk: 20.1 nmol/L	Vit D 1000 IU/d 3 rd trimester only	nd	First generation Asian immigrants only
El-Hajj 2006 ⁴⁸ Lebanon (33°N) [16278262]	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	<p>healthy</p> <p>13.2 (10–17)</p> <p>0</p>	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
Mallet 1986 ⁵³ France (48° N) [3755517]	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	<p>pregnancy</p> <p>newborn</p> <p>nd</p>	Ca intake 550 to 1000 mg/d in 55% of the subjects	Vit D 1000 IU/d vs. 200,000 IU 1x dose	nd	
Radioimmunoassay						
Wagner 2006 ⁵² Charleston, US (32°N) [17661565]	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	<p>Fully lactating; <1 mo postpartum</p> <p>29</p> <p>0</p>	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
Hollis, 2011 ¹ Charleston, US	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	<p>Healthy</p> <p>27 (18–41/5.6)</p> <p>0%</p>	<p>serum: delivered group- 59.5 23.8 nmol/L (6.0–172.5) exited group- 50.5 25.1 nmol/L (6.5–120.5)</p> <p>vit D intake: 400 IU group- 181.6 +/- 108.4 IU/d, 2000 IU group- 195.8 +/- 135.0, 4000 IU group- 204.2 +/-148.2</p> <p>calcium intake: 400 IU group-1063.6 +/-539.6 mg/d, 2000 IU group- 993.9 +/-514.0 mg/d, 4000 IU group- 1073.6+/- 491.9 mg/d</p>	<p>Birth weight:</p> <p>Vit D 4000 IU vs.</p> <p>Vit D 2000 IU vs.</p> <p>Vit D 400 IU</p>	<p>69% (400-IU group), 68% (2000-IU group), and 69% (4000-IU group, p¼0.9)</p>	Assignment to the interventions was only partially random: Baseline serum 25(OH)D also partly determined assignment

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Kalra, 2012 ⁴³ India	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	nd 26.7 (SD 4.0) 0%	Table 2: Group 1–31.7 nmol/L (14.0–57.2) Group 2– 32.0 nmol/L (14.5–45.7)	Birth weight: nd 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester) Length at Birth: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester)	age= Group 1 from table 2
Roth 2013 ⁴⁴ Bangladesh	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	Healthy 22.4 (SD 3.5) 0%	Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l	Birth weight: 99.2 ± 2.7% 35000 IU Vit D3 3rd trimester vs. Placebo Length at birth: 35000 IU Vit D3 3rd trimester vs. Placebo	
Wagner 2013 ⁴² US	<ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) 	nd 27 (18–41) 0%	61.5 nmol/L	2000 IU vit D3 vs. 4000 IU vit D3 vs. control	NR

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Assay method not reported						
Marya 1981 ⁵⁴ India (28°N) [7239350]	<ul style="list-style-type: none"> • Health status 	no pregnancy- related complications	Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d	Vit D 1200 IU/d + Ca 375 mg/d (3 rd trimester) or Vit D 1.2 mil IU (total; 600,000 IU in 7 th & 8 th mo) or no supplement	nd	
Marya 1988 ⁵⁰ India (28°N) [3243609]	<ul style="list-style-type: none"> • 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 7 th & 8 th mo) vs. no supplement	nd	
Feliciano 1994 ⁴⁹ China (22°N to 47°N) [8078115]	<ul style="list-style-type: none"> • 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	

Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)

Table of Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)						Confounders/Effect Modifiers Adjusted						Comments
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle		
Radioimmunoassay												
Morley 2006 ⁵⁶ Australia (38°S) [16352684]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	singleton pregnancy; no disease 29 0	<ul style="list-style-type: none">• 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 ⁵⁵ PAHSG UK (50°N) [17311057]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	singleton pregnancy <17 wk 26.3 0	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA nd	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only
Radioimmunoassay and chemiluminescence assay averaged together												
Burris 2012 ⁴⁵ Massachusetts, US	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	nd 33 (SD 4.5) 0%			Weight in offspring stratified by mother's 25(OH)D		X	X		X		
HPLC and tandem mass spectrometry												
Gernand, 2013 ⁴⁶ US	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	Singleton gestation nd 0%			Weight in offspring stratified by mother's 25(OH)D		X	X		X	X	

Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report)

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Radioreceptor assay														
Maxwell 1981 ⁵¹ Brooke 1980 ⁴⁷ [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, 32 77	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					
El-Hajj 2006 ⁴⁸ [16278262]	9–18 y female, premenar che	Height	2°	1 y	Vit D ₃ 2000 IU	nd, ≤34 total	%	nd	5.60%	~4.8, 6.4 ^C	~1.8%	~0.6, 3.0 ^C	0.07	C
Vit D ₃ 200 IU							nd	5.00%	~4.2, 5.8 ^C	~1.2%	~0.01, 2.4 ^C			
Placebo							nd	3.80%	~0.9, 6.7 ^C					
Weight		2°	1 y	Vit D ₃ 2000 IU	nd, ≤34 total	%	nd	18.40%	~14.7, 22.1 ^C	~3.5%	~1.3, 8. 3 ^C			
				Vit D ₃ 200 IU			nd	15.30%	~12.5, 18.1 ^C	~0.4	-3.7, 4.5 ^C			
				Placebo			nd	14.90%	~11.8, 18.0 ^C					
Mallet 1986 ⁵³ France (48° 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)										
Radioimmunoassay														
Wagner 2006 ⁵² [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, 81 00	Diff -800	-2300, 7 00 ^C	0.3	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	
		Mother (6400)	9				NA	69.3	67.4,					

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					+infant (0)					71.2				
Hollis 2011 ¹	Pregnant or lactating women	Birth weight	2°	Delivery	Vit D 4000 IU	117	g	NR	Final 3284.6	3175.2, 3394.0	+62.8	-103.4, 229.0	0.23	A
					Vit D 2000 IU	122			Final 3360.1	3255.2, 3465.0	+138.3	-24.4, 301.0		
					Vit D 400 IU	111			Final 3221.8	3094.9, 3348.8				
Kalra 2012 ⁴³	Pregnant or lactating women between 12–24 weeks gestation	Birth weight	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	kg	NR	Final 3.03	1.71, 4.35	-0.05	-1.92, 1.82	0.96	C
					1500 mg cholecalciferol (one dose 2nd trimester)	36	kg		Final 3.08	1.71, 4.45				
		Length at birth	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	cm	NR	Final 50.1	49.8, 50.4	-0.2	-0.6, 0.2	0.35	
					1500 mg cholecalciferol (one dose 2nd trimester)	36	cm		Final 50.3	50.0, 50.6				
Roth 2013 ⁴⁴		Birth weight	2°	Delivery	35000 IU Vit D ³ 3rd trimester	73	g	NR	Final 2802	2675, 2929	+14	-138, 166	0.86	A
					Placebo	74	g		Final 2788	2700, 2876				
		Length at birth	2°	Delivery	35000 IU Vit D ³ 3rd trimester	73	cm	NR	Final 48.2	47.6, 48.8	+0.2	-0.5, 0.9	0.55	
					Placebo	74	cm		Final 48	47.5, 48.5				
Wagner 2013 ⁴²		neonatal birth weight	1°		2000 IU vit D ³	201	g	NR	Final 3382	sd=759	+149	-21, 319	0.09	B
					4000 IU vit D ³	193			Final 3231	sd=632	-2	-154, 150	0.98	
					control	110			Final 3233	sd=668				

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality	
Assay method not reported															
Marya 1981 ⁵⁴ [7239350] ^E	Pregnant women & infant 0–6 mo	Birth weight	2°	Delivery	Vit D 1.2 mil IU total	20	g	NA	Final 3140	2940, 3340	Diff 410	166, 654 ^C	0.00 1	C	
					Vit D 1200 IU + 375 mg Ca (3 rd trimester)	25	g	NA	Final 2890	2760, 3020	Diff 160	0, 320 ^C	0.05		
					No supplement	75		NA	2730	2650, 2810					
Marya 1988 ⁵⁰ India [3243609]	Pregnant women & infant 0–6 mo	Birth weight	1°	Delivery	Vit D 1.2 mil IU total	100	g	NA	Final 2990	2920, 3060	Diff 190	90, 290 ^C	<0.0 01	C	
					No supplement	100		NA	2800	2730, 2870					
		Birth length	2°		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	<0.0 01		
					No supplement	100		NA	48.45	48.1, 48.8					
Feliciano 1994 ⁴⁹ [8078115]	0–6 mo	Weight gain born in spring, N. China ^A	1°	6 mo	Vit D 400 IU	12	g	nd	3745	2613, 48 77	-463	-1852, 9 26 ^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	18.1, 19.9	-0.3	-2.2, 1.6 ^C	NS		
					Vit D 100 IU	15		nd	19.3	17.6, 21.0					

^ASee Table 1 in original paper for complete results stratified by North vs. South China and birth in spring vs. fall

^BSee Table 3 in original paper for results on 1 mo and 4 mo

^CEstimated from available data

^DEstimated from number of mothers; number of infants not reported

^EThis 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 (updated from original report)

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
Radioimmunoassay									
Morley 2006 ⁵⁶ 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 ⁵⁵ 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	3.4	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	
				30–150	nd	15.8	1.26		
				50–175	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	0.1	
				30–150	nd	29.4	1.21		
				50–175	nd	30	1.2		
				>75	nd	29.3	1.19		
	Pregnant women; infant 0–16 mo	Birth length (N=466)	Delivery	<30	nd	50 cm	1.83	0.15	
				30–150	nd	50	2.29		
				50–175	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	
				30–150	nd	71.4	2.6		
				50–175	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	
				30–150	nd	131.5	6.66		
				50–175	nd	131.8	5.09		
				>75	nd	130.6	6.45		

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
Radioimmunoassay and chemiluminescence assay averaged together									
Burris 2012 ⁴⁵ and Burris averaged together	Pregnant or lactating women	Birth weight	Delivery	<25	47	3.46kg	SD=0.68	ND	A
				25–150	314	3.55kg	SD=0.52		
				50–175	543	3.53kg	SD=0.51		
				≥75	229	3.51kg	SD=0.52		
HPLC and tandem mass spectrometry									
Gernand 2013 ⁴⁶	singleton gestation	Birth weight	Delivery	<37.5	747	3127g	SD=15	0.014	B
				≥37.5	1399	3215g	SD=11		

Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioimmunoassay						
Lappe 2007 ¹⁰² Nebraska, US (41° N) [17556697]	<ul style="list-style-type: none"> • 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	
Other or not reported						
Trivedi 2003 ⁶⁶ Oxford, UK (52°N) [12609940]	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	General population 75 (65–185) 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%

^ANo difference between the vitamin D and the placebo arm.

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report)

Table 101 Vitamin D and total cancer mortality: Characteristics of cohort studies (updated from original report)						Confounders/Effect Modifiers Adjusted						
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons		Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Comments
Radioimmunoassay												
Freedman 2007 ¹⁰³ NHANES III US (various) [16481636]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Any 44 (≥17) 45	<ul style="list-style-type: none">• 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 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	<ul style="list-style-type: none">• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Freedman, 2010 ¹⁰⁰ US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 44.5 87.8%			Total cancer mortality stratified by baseline 25(OH)D sextiles		X	X		X	X	age, race, %female for lowest group of table 1
Tomson 2013 ⁷⁵ Whitehall study London, UK	<ul style="list-style-type: none">• Health status• Mean age• Male (%)	Self-reported 76.9 (4.9) 100%			Cancer mortality stratified by baseline 25(OH)D category			X	X		X	
Chemiluminescence Assay												
Eaton, 2011 ⁷⁰ US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 65.1 (7.6) 0%			Cancer mortality stratified by baseline 25(OH)D quartiles			X	X	X	X	
Signorello, 2013 ⁷⁴ Southern Community Cohort Study US	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd nd nd						X			X	

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 62 (SD 6.5) 43.8%	Cancer mortality stratified by baseline 25(OH)D tertiles	X	X		X	X	X	
Afzal 2013 ⁹⁹ Denmark	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR 58 (47–165)	Cancer mortality stratified by baseline 25(OH)D category		X	X			X	
Ordonez-Mena ⁹⁷ Saarland. Germany	<ul style="list-style-type: none"> • Health status • Mean age • Male (%) 	NR nd NR (50–174) 54%	Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X			X	
Enzyme-linked Immunoabsorption Assay										
Hutchinson, 2010 ⁷⁹ Tromso Tromso, Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd nd	Cancer mortality stratified by baseline 25(OH)D quartiles		X	X	X		X	
Lin, 2012 ⁸³ Linxian, China	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, Hypertension 56.5 (SD 7.9) 55%	Cancer mortality stratified by baseline 25(OH)D tertiles		X	X	X		X	

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
HPLC-Tandem Mass Spectrometry											
Michaelsson, 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	More than 1/3 being treated for hypertension 71 (SD 0.6) 100%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X	X	X	X	Three multivariate models. The most complex model accounted for a range of chronic diseases, supplemental vitamin D use, fish intake, vitamin D intake, C-reactive protein, troponin, triglycerides, HDL cholesterol, retinol, insulin, total energy intake, alcohol intake, lipid lowering treatment, hypertension treatment
Cawthon, 2010 ⁹⁸ MrOS	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	>80% excellent/good health status 74 (≥65) 100%		Cancer mortality stratified by baseline 25(OH)D quartiles and tertiles	X	X	X	X	X	X	MrOS study
de Boer, 2012 ⁸⁷ US (various)	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 74 (SD 4.6) 30%		Cancer stratified by baseline 25(OH)D median		X	X	X		X	
New Nested case-control study											
Enzyme-linked Immunoabsorption Assay											
Fedirko, 2012 ¹⁰¹ EPIC Multiple Countries	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 62.1 (SD 7.2) 40.5%				X	X	X	X	X	age, %female= quintile 1

Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report]

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
Radioimmunoassay												
Lappe 2007 ¹⁰²	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
Nebraska, US (41° N)					Ca (citrate 1400 mg or carbonate 1500 mg)	17	445					
[17556697]	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					
Other or not reported												
Trivedi 2003 ⁶⁶	65–185 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
[12609940]					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 and total cancer mortality: Results of cohort studies (updated from original report)

Author Year	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
[PMID]										
Radioimmunoassay										
Freedman 2007 ¹⁰³	Adults, both sexes	Cancer mortality (536/16818; 0.032)	105 mo	<50	175	5744	1	Reference	0.65	B
NHANES III				50 to <62.5	103	3143	1.22	0.91, 1.64		
US				62.5 to <80	117	3713	1.02	0.69, 1.50		
[16481636]				80 to <100	80	4218 (total, ≥80 nmol/L)	1	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	1.4	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 ⁸⁵	Adults, both sexes	Cancer mortality (N=13331)	Median 8.7 (IQR 7.1– 110.2) y	>80	nd	nd	1	Reference	nd	C
NHANES III				61–180	nd	nd	0.8	0.54, 1.19		
US (various)				44–160	nd	nd	1.08	0.8, 1.46		
[18695076]				<44	nd	nd	0.91	0.63, 1.31		

Author Year	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
[PMID]										
Freedman 2010 ¹⁰⁰	men & women, all seasons	total cancer mortality	13.4 yrs	< 37.5 nmol/L	116	2689	RR = 1	Reference	0.43	B
NHANES III US (multisite)				37.5–1<50 nmol/L	174	3056	1.04	0.77, 1.41		
				50–<62.5 nmol/L	165	3143	1.23	0.89, 1.69		
				62.5–180 nmol/L	200	3713	1.19	0.86, 1.65		
				80–1<100 nmol/L	139	2521	1.12	0.80, 1.57		
				≥100 nmol/L	90	1697	1.15	0.79, 1.68		
men & women, winter/lower latitude	total cancer mortality	< 37.5 nmol/L	55	2689	1.00	Reference	0.23			
		37.5–1<50 nmol/L	79	3056	1.3	0.77, 2.19				
		50–<62.5 nmol/L	57	3143	1.2	0.64, 2.26				
		62.5–180 nmol/L	78	3713	1.67	0.98, 2.86				
		80–1<100 nmol/L	54	2521	1.31	0.77, 2.23				
		≥100 nmol/L	32	1697	1.5	0.74, 3.02				
men & women, summer/ higher latitude		< 37.5 nmol/L	61	2689	1.00	Reference	0.67			
		37.5–1<50 nmol/L	95	3056	0.91	0.63, 1.32				
		50–<62.5 nmol/L	108	3143	1.19	0.78, 1.82				
		62.5–180 nmol/L	122	3713	1.02	0.67, 1.54				
		80–1<100 nmol/L	85	2521	1.03	0.66, 1.63				
		≥100 nmol/L	58	1697	1.02	0.63, 1.45				
men, all seasons		< 37.5 nmol/L	47	2689	1.00	Reference	0.09			
		37.5–1<50 nmol/L	95	3056	1.66	0.98, 2.80				
		50–<62.5 nmol/L	90	3143	1.43	0.90, 2.26				
		62.5–180 nmol/L	122	3713	1.52	0.82, 2.80				
		80–1<100 nmol/L	90	2521	1.66	1.06, 2.61				
		≥100 nmol/L	69	1697	1.85	1.02, 3.35				
men, winter/lower latitude		< 37.5 nmol/L	25	2689	1.00	Reference	0.55			
		37.5–1<50 nmol/L	51	3056	2.58	1.37, 4.87				
		50–<62.5 nmol/L	31	3143	1.14	0.48, 2.70				
		62.5–80 nmol/L	52	3713	1.99	0.86, 4.13				
		80–<100 nmol/L	33	2521	1.42	0.74, 2.72				
		≥100 nmol/L	23	1697	1.94	0.69, 5.45				
men,			< 37.5 nmol/L	22	2689	1.00	Reference	0.045		

Author Year		Outcome	Followup Duration								
Study Name	Life Stage	(n/N; Incidence)	(Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality	
[PMID]											
	summer/higher latitude			37.5-<50 nmol/L	44	3056	1.28	0.51, 3.23			
				50-<62.5 nmol/L	59	3143	1.55	0.81, 2.99			
				62.5-180 nmol/L	70	3713	1.33	0.53, 3.53			
				80-1<100 nmol/L	57	2521	1.76	0.87, 3.57			
				≥100 nmol/L	46	1697	1.84	0.85, 3.98			
	women, all seasons			< 37.5 nmol/L	69	2689	1.00	Reference			0.29
				37.5-1<50 nmol/L	79	3056	0.85	0.59, 1.22			
				50-<62.5 nmol/L	75	3143	1.25	0.82, 1.90			
				62.5-180 nmol/L	78	3713	1.11	0.69, 1.79			
				80-1<100 nmol/L	49	2521	0.86	0.50, 1.46			
	women, winter/lower latitude			≥100 nmol/L	21	1697	0.64	0.35, 1.18			
				< 37.5 nmol/L	30	2689	1.00	Reference			0.42
				37.5-1<50 nmol/L	28	3056	0.74	0.36, 1.51			
				50-<62.5 nmol/L	26	3143	1.27	0.51, 3.18			
				62.5-180 nmol/L	26	3713	1.44	0.61, 3.38			
	women, summer/higher latitude			80-1<100 nmol/L	21	2521	1.28	0.50, 3.24			
				≥100 nmol/L	9	1697	1.01	0.26, 3.90			
				< 37.5 nmol/L	39	2689	1.00	Reference			0.03
				37.5-1<50 nmol/L	51	3056	0.88	0.54, 1.43			
				50-<62.5 nmol/L	49	3143	1.18	0.65, 2.12			
				62.5-180 nmol/L	52	3713	0.99	0.52, 1.87			
				80-1<100 nmol/L	28	2521	0.7	0.34, 1.44			
				≥100 nmol/L	12	1697	0.52	0.25, 1.10			
Tomson 2013 ⁷⁵ Whitehall study		Death, cancer	13.1 yrs	Doubling Concentration	809	5409	0.84	0.71, 1.00		B	
Chemiluminescence Assay											
Eaton 2011 ⁷⁰	Postmenopausal women	cancer mortality	10 yrs	Q 1: 3.25-136.50 nmol/L	nd	608	1.39	0.88, 2.19	0.11	A	
WHI US (multisite)				Q 2: 36.51-149.95 nmol/L	nd	606	1.22	0.79, 1.89			
				Q 3: 49.96-165.38 nmol/L	nd	608	1.12	0.72, 1.72			
				Q 4: 65.39-1146.67 nmol/L	nd	607	1.00	Reference			
Signorello 2013 ⁷⁴	Men and women (40-179 years,	cancer death	NR	Quartile 4: (>54.1 nmol/L)	115	228	OR = 1	Reference	0.53	A	

Author Year		Outcome	Followup Duration							
Study Name	Life Stage	(n/N; Incidence)	(Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
[PMID]										
Southern Community Cohort Study	2/3 African American)			Quartile 3: 37.9–1>54.1 nmol/L)	102	228	OR = 0.79	0.52, 1.21		
				Quartile 2: (25.45–37.9 nmol/L)	127	255	OR = 1.03	0.66, 1.59		
				Quartile 1: <25.45 nmol/L)	133	243	OR = 1.28	0.78, 2.11		
Schottker 2013 ⁷⁶ ESTHER		cancer mortality	9.5 yrs	<30	90	1439	1.42	1.08, 1.87		B
				30–150	172	4188	1.04	0.83, 1.29		
				>50	171	3927	1.00	Reference		
Afzal 2013 ⁹⁹		all cancer	28 yrs	50% reduction in plasma levels	2488	9791	1.06	1.02, 1.11		B
Ordonez-Mena ⁹⁷		total cancer	8 yrs	Q1	235	2253	1.10	0.93, 1.30		B
				Q2+Q3	396	4500	1.00	Reference		
				Q4	242	2254	1.12	0.95, 1.32		
Enzyme-linked Immunoabsorption Assay										
Hutchinson 2010 ⁷⁹ Tromsø Study Norway	Men (55–174 years) Women (50–174 years)			Quartile 1: mean=33.8 (sd=7.6)	72	1184	1.14	0.80–11.63	NR	
				Quartile 2: mean=46.7 (sd=6.0)	69	1187	1.13	0.80–11.61		
				Quartile 3: mean=56.2 (sd=6.0)	74	1192	1.23	0.87–11.75		
				Quartile 4: mean=72.3 (sd=13.2)	58	1188	1.00	Reference		
	non-smokers	cancer mortality	11.7 yrs	Quartile 1: mean=33.8 (sd=7.6)	55	597	0.82	0.56–11.21	NR	B
				Quartile 2: mean=46.7 (sd=6.0)	54	606	0.86	0.59–11.26		
				Quartile 3: mean=56.2 (sd=6.0)	60	607	1.02	0.70–11.48		
				Quartile 4: mean=72.3 (sd=13.2)	56	600	1.00	Reference		
	smokers			continuous 25(OH)D	217	1101	0.97	0.89, 1.05	0.406	
				continuous 25(OH)D	141	608	1.00	0.91, 1.10		
				continuous 25(OH)D	76	493	0.88	0.75, 1.03		
				continuous 25(OH)D						
Lin 2012 ⁸³ General Population Trial of Linxian China	Men (40–169 years)	cancer deaths	24 yrs	continuous 25(OH)D	141	608	1.00	0.91, 1.10	0.967	B
	women			continuous 25(OH)D	76	493	0.88	0.75, 1.03		
				continuous 25(OH)D						

Author Year		Outcome	Followup Duration							
Study Name	Life Stage	(n/N; Incidence)	(Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
[PMID]										
HPLC-Tandem Mass Spectrometry										
Michaelsson 2010 ⁸⁴				< 10th percentile (<46 nmol/L)	27	119	1.99	1.29, 3.08		
Uppsala Longitudinal Study of Adult Men Sweden	Elderly men (mean age 71)	cancer mortality	12.7 yrs	10th–190th percentile (46–193 nmol/L)	118	956	1.00	Reference		B
				>90th percentile (>93 nmol/L)	19	119	1.56	0.95, 2.56		
Cawthon 2010 ⁹⁸	Men 65 and over			Q 1: <49.8 nmol/L	NR	372	0.52	0.27, 1.00	0.086	
MrOS US (6 sites)				Q 2: 49.8≥ to <63 nmol/L	NR	370	0.90	0.51, 1.60		
				Q 3: ≥63to <75 nmol/L	NR	372	0.80	0.45, 1.41		
		cancer mortality	7.3 yrs	Q 4: ≥75 nmol/L	NR	376	1.00	reference		B
				Deficient, <50 nmol/L	NR	376	0.51	0.27, 0.98	0.044	
				Insufficient, 50 to <75 nmol/L	NR	737	0.85	0.52, 1.40		
				Sufficient, ≥75 nmol/L	NR	377	1.00	reference		
				per SD decrease	NR	1490	0.80	0.64, 0.99	NR	
de Boer 2012 ⁸⁷	Adults 65 and over	cancer	11 yrs	Normal level	259	1126	1.00	Reference	NR	A
Cardiovascular Health Study US (4 sites)				Low level (season specific, ranges 43–161 nmol/L)	111	495	1.13	0.90, 1.42		
NEW Nested case-control study										
Enzyme-linked Immunabsorption Assay										
Fedirko 2012 ¹⁰¹				<36.3	104	242	1.00	Reference	0.04	B
EPIC	Men and women (age at diagnosis approximately 62)	colorectal cancer specific mortality	73 mos	36.4–48.6	85	239	0.76	0.56, 1.02		
Europe (multinational)				48.7–60.5	95	241	0.93	0.69, 1.24		
				60.6–76.8	78	240	0.78	0.58, 1.06		
				>76.8	82	240	0.69	0.50, 0.93		

* Statistically significant (P<0.05)

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

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		
Cohort Studies											
Radioreceptor Assay											
Corder 1993 ¹¹⁴ San Francisco US (37°N) [8220092]	Health status	nd	Assay	Competitive protein-binding (Haddad, 1971)	Prostate cancer risk compared by baseline 25(OH)D		X			X	50% black; 50% white
	Mean age (range/SD), y	57 (38–81)									
	Male (%)	100	Season blood drawn	nd							
Nomura 1998 ¹¹⁸ Honolulu Heart US (21°N) [9794175]	Health status	64% smoked	Assay	Protein-binding	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	100% Japanese Americans
	Mean age (range/SD), y	58 (49–70)									
	Male (%)	100	Season blood drawn	nd							
Baron 2005 ¹¹² CPP US (multiple latitudes) [15767334] ^B	Health status	had >1 colon adenoma removal	Assay	Competitive protein-binding (Quest)	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X	5% black
	Mean age (range/SD), y	62 (8.7)									
	Male (%)	100	Season blood drawn	nd							
Radioimmunoassay											
Ahn 2008 ¹¹⁰ PLCO US (21°N to 44°N) [18505967]	Health status	8% current smoker	Assay	RIA (Heartland)	Prostate cancer risk stratified by baseline 25(OH)D quintiles	X		X	X		X
	Mean age (range/SD), y	67.8 (5.3)									
	Male (%)	100	Season blood drawn	nd							
Platz 2004 ¹¹⁹ Mikhak 2007 ¹¹⁷ HPFS US	Health status	Smoked 18%; DM 3.6%	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	6% nonwhite
	Mean age (range/SD), y	66 (7)									

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	
(multiple latitudes) [15090720] [17440943]	Male (%)	100	Season blood drawn	nd								
Freedman 2007 ¹⁰³ NHANES III US (multiple latitudes) [17971526]	Health status	28% current smoker	Assay	RIA	Prostate cancer mortality stratified by 2 baseline 25(OH)D categories	X	X	X	X	X	X	71% white; 14% black; 6% Hispanics
	Mean age (range/SD), y	44										
	Male (%)	100	Season blood drawn	South: Nov to Mar; North: Apr to Oct								
Tuohimaa 2004 ¹²⁰ Helsinki Heart Vasterbotten; Janus Project; Finland (60°N) [14618623]	Health status	Gemfibrozil vs. placebo subjects <40 to >60	Assay	RIA (Incstar)	Prostate cancer risk stratified by 5 baseline 25(OH)D categories		X			X		
	Mean age (range/SD), y											
	Male (%)	100	Season blood drawn	nd								
Li 2007 ¹¹⁶ Gann 1996 ¹²² PHS US (multiple latitudes) [17388667] [8850273]	Health status	on ASA, β - carotene, placebo trial; 9% current smoker	Assay	RIA (Bruce Hollis)	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X				X	94% white
	Mean age (range/SD), y	58.9 (8.3)										
	Male (%)	100	Season blood drawn	24% spring or winter								
Ahonen 2000 ¹¹¹ Helsinki Heart Finland (60°N) [11075874]	Health status	Gemfibrozil vs. placebo subjects 40–57	Assay	RIA (Incstar)	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X	X	X	X	
	Mean age (range/SD), y											
	Male (%)	100	Season blood drawn	Jan-Feb; Mar- May; Sep								
Tuohimaa 2007 ¹²¹ Helsinki Heart Finland (60°N)	Health status	Gemfibrozil vs. placebo subjects	Assay	RIA (Incstar)	Prostate cancer risk stratified by 3 baseline 25(OH)D categories		X	X	X			
	Mean age (range/SD), y	51 (3.7)										

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	
17301263	Male (%)	100	Season blood drawn	Most in winter							
Jacobs 2004 ¹¹⁵ NPC Eastern US (25°46'N to 41°N) [15225833]	Health status	Selenium vs. placebo subjects ^A 68 (nd)	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D tertiles		X	X	X	X	
	Mean age (range/SD), y										
	Male (%)	100	Season blood drawn	nd							
Braun 1995 ¹¹³ WCC, MD US (39°N) [7612803]	Health status	nd	Assay	RIA (Bruce Hollis, 1993)	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X				100% white
	Mean age (range/SD), y	<45–75+									
	Male (%)	100	Season blood drawn	Aug through Nov							
Nested case-control studies											
Radioimmunoassay											
Shui, 2012 ¹⁰⁸ Health Professionals' Followup Study US	Health status	nd			Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	
	Mean age (SD), y	64.4 (SD 7.8)									
	Male (%)	100%									
	Mean age (range/SD), y	73.6 (5.9)									
	Male (%)	100%									
Enzyme-linked Immunoabsorption Assay											
Park, 2010 ¹⁰⁷ Multiethnic Cohort Study	Health status	nd			Prostate cancer risk stratified by baseline 25(OH)D quartiles	X		X			
	Mean age (SD), y	68.7 (SD 7.2)									
	Male (%)	100%									

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	
Travis 2009 ¹⁰⁹ European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	Health status Mean age (SD), y Male (%)	nd 60.5 (SD 6.2) 100%	Prostate cancer risk stratified by baseline 25(OH)D		X	X			X	
Ordonez-Mena 2013 ⁹⁷ ESTHER Saarland, Germany	Health status Mean age Male (%)	NR 50–74 54%	Cancer mortality stratified by baseline 25(OH)D tertiles	X		X	X			confounders- add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer
HPLC-Tandem Mass Spectrometry										
Barnett, 2010 ¹⁰⁴ MrOS US (various)	Health status Mean age (range/SD), y Male (%)	nd 73.6 (5.9) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	
Brandstedt, 2012 ¹⁰⁵ Malmo, Sweden	Health status Mean age (range), y Male (%)	nd 61.7 (NR, SD 6.4) 100%	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X			X	Malmo Diet and Cancer Study (MDCS)
Meyer, 2013 ¹⁰⁶ Norway	Health status Mean age (range), y Male (%)	nd 48.2 (SD 9.2) 100%	Prostate cancer risk stratified by baseline 25(OH)D sextiles		X			X		

^AFor prevention of recurrence of non-melanoma skin cancer.

^BThis is a cohort study, not a nested case-control study.

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report)

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
Cohort Studies										
Radioreceptor Assay										
Corder 1993 ¹¹⁴ [8220092]	19–50 51–70	Prostate cancer (181; 181) Mortality prostate cancer	>5 (mode)	60.0 (case) vs. 50.5 (control) (est.) nd	181 51	181 nd	- -	- -	- -	C
Nomura 1998 ¹¹⁸ Honolulu Heart [9794175]	19–50 51–70	Prostate cancer (136; 136)	16 (mean)	<85 ^D 85–101 102–119 ≥120	38 35 30 33	34 36 32 34	1 0.8 0.8 0.8	Reference 0.4, 1.8 0.4, 1.7 0.4, 1.8	0.68	C
Baron 2005 ¹¹² CPP [15767334] ^F	19–50 51–70	Prostate cancer (70 cases in a total of 672) ^F	<4 (34%)	<62.9 62.9–84.9 85	nd nd nd	NA NA NA	1 1.22 0.32	Reference 0.66, 2.26 0.72, 2.43	0.7	C
Radioimmunoassay										
Ahn 2008 ¹¹⁰ PLCO [8505967]	51–70	Prostate cancer (741; 781)	2–8	12.8–42.5 42.5–51. 51.4–60.5 60.6–71.7 71.8–129.5	119 125 190 167 148	157 156 157 156 155	1 1.1 1.53 1.33 1.18	Reference 0.78, 1.56 1.10, 2.13* 0.95, 1.86 0.83, 1.68	0.2	B
Platz 2004 ¹¹⁹ Mikhail 2007 ¹¹⁷ HPFS [15090720] [17440943]	51–70	Prostate cancer (460; 460)	2.2 (mean)	Quartile 1 ^A Quartile 2 Quartile 3 Quartile 4	109 115 94 142	114 113 120 113	1 1 0.77 1.19	Reference 0.67, 1.49 0.51, 1.15 0.79, 1.79	0.59	B
Freedman 2007 ¹⁰³ NHANES III [17971526]	19–50	Mortality prostate cancer	nd	<62.5 ≥62.5	22 25	nd nd	1 0.91	Reference 0.39, 2.14	0.95	B
Tuohimaa 2004 ¹²⁰ Helsinki Heart [14618623]	19–50 51–70	Prostate cancer (622; 1451)	≤9 →14 (range)	≤19 20–39 40–59 60–79 ≥80	19 169 229 138 67	nd nd nd nd nd	1.5 1.3 1 1.2 1.7	0.8, 2.7 0.98, 1.6 Reference 0.9, 1.5 1.1, 2.4*		C

Author Year										
Study Name	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
PMID										
Li 2007 ¹¹⁶ 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	0.71, 1.41		
				Quartile 4	nd	nd	1	Reference		
Gann 1996 ¹²² PHS [8850273]	19–50 51–70	Prostate cancer (232; 414)	6 (mean)	15.7–53.3	nd	nd	1	nd	0.82	C
				53.4–70.9	nd	nd	1.1	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	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	nd	nd		
			53.4–70.9	nd	nd	1	nd			
			71–93.5	nd	nd	0.82	nd			
			93.6–194	nd	nd	0.76	0.39, 1.47			
Ahonen 2000 ¹¹¹ 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				
Tuohimaa 2007 ¹²¹ 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 ¹¹⁵ 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		

Author Year	Life Stage	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	
Study Name	(male), y										
PMID											
Braun 1995 ¹¹³				<60.1	7	24	1	Reference			
WCC	19–50	Prostate cancer	14 (mean)	60.1–73.8	17	25	2.3	0.7, 7.8	0.6	C	
[7612803]	51–70	(61; 122)		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			
Nested case-control studies											
Radioimmunoassay											
Shui 2012 ¹⁰⁸				Quartile 1	41	325	1.00	Reference		A	
Health Professionals' Followup Study	Lethal Prostate Cancer (209;1324)	5.2 years	Quartile 2	33	336	0.78	0.47, 1.30		0.002		
			Quartile 3	21	334	0.50	0.28, 0.88				
			Quartile 4	19	329	0.44	0.24, 0.79				
			Quartile 1	310	325	1.00	Reference				
	Overall Prostate Cancer (1260;1324)	5.2 years	Quartile 2	298	336	0.93	0.74, 1.17		0.45	A	
			Quartile 3	319	334	0.99	0.79, 1.24				
			Quartile 4	333	329	1.07	0.86, 1.34				
			Quartile 1	51	325	1.00	Reference				
	Advance stage at Diagnosis (166;1324)	5.2 years	Quartile 2	43	336	0.96	0.61, 1.52		0.22		
			Quartile 3	32	334	0.63	0.39, 1.03				
			Quartile 4	40	329	0.85	0.53, 1.35				
			Quartile 1	69	325	1.00	Reference				
High Grade Prostate Cancer (239;1324)	5.2 years	Quartile 2	55	336	0.81	0.54, 1.21		0.87			
		Quartile 3	51	334	0.75	0.50, 1.13					
		Quartile 4	64	329	0.99	0.67, 1.46					
		Enzyme-linked Immunoabsorption Assay									
Park 2010 ¹⁰⁷				Quartile 1: <57.3 nmol/L	82	163	1.00	Reference			
multiethnic cohort	Men 45–75 yrs	Prostate Cancer (329, 656)	NR	Quartile 2: 57.3 <77.5 nmol/L	84	166	1.05	0.70, 1.58		0.600	A
				Quartile 3: 77.5<99.8 nmol/L	72	172	0.81	0.52, 1.28			
				Quartile 4: ≥99.8 nmol/L	91	155	1.17	0.72, 1.89			
				Deficient: <50nmol/LL	53	106	1.10	0.68, 1.78			
				Insufficient: 50–75 nmol/L	98	204	1.04	0.73, 1.48			

Author Year	Life Stage	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		
Study Name	(male), y											
PMID												
				75–125 nmol/L	137	287	1.00	Reference				
				≥125 nmol/L	41	59	1.52	0.92, 2.51	0.320			
Travis 2009 ¹⁰⁹		Prostate Cancer	4.1 years	Quintile 1 (2.5–40.4nmol/L)	125	151	1.00	Reference				
European Prospective Investigation into Cancer and Nutrition (EPIC)				Quintile 2(40.5–50.4 nmol/L)	143	150	1.27	0.89, 1.81		A		
				Quintile 3(50.5–59.1nmol/L)	128	151	1.23	0.85, 1.76				
				Quintile 4 (59.2–70.8nmol/L)	114	150	1.06	0.73, 1.55				
				Quintile 5(70.9–163.7nmol/L)	142	150	1.28	0.88, 1.88				
				Doubling Concentration	652	752	1.17	0.93, 1.47	0.188			
Ordonez-Mena 2013 ⁹⁷		Prostate Cancer	8 yrs	Q1	38	882	HR 1.16	0.78, 1.74		B		
ESTHER				Q2+Q3	66	1737	HR 1.00	Reference				
				Q4	67	1505	HR 1.21	0.86, 1.70				
HPLC-Tandem Mass Spectrometry												
Barnett 2010 ¹⁰⁴	men 65 and over	Prostate Cancer (297 cases in a total of 1648)	NR	Quartile 1(7.75–49.75 nmol/L)	68	411	HR=1.00	Reference		B		
MrOS												
				Quartile 2(50.0–62.3 nmol/L)	91	415	1.35	0.91, 2.01	0.130			
				Quartile 3(62.5–74.8 nmol/L)	53	406	0.64	0.41, 1.00	0.050			
				Quartile 4 (75–189.0 nmol/L)	85	416	1.20	0.81, 1.78	0.370			
Brandstedt 2012 ¹⁰⁵ [HPLC only]	51–70 yrs; ≥71 yrs	Prostate Cancer (918; 924)	NR	Quartile 1 (≤68nmol/L)	206	242	1.00	Reference		A		
				Quartile2(69–84nmol/L)	237	232	1.25	0.95, 1.65				
				Quartile3(85–102nmol/L)	245	226	1.37	1.03, 1.82				
				Quartile 4(≥103nmol/L)	230	224	1.34	0.99, 1.82	0.048			
Meyer 2013 ¹⁰⁶		Prostate Cancer (2106;2106)	NR	<30nmol/L	72	92	IRR=0.82	0.58, 1.15		B		
				30–49nmol/L	528	553	1.02	0.87, 1.21				
				50–69nmol/L	718	771	1.00	Reference				
				70–89nmol/L	537	466	1.24	1.05, 1.47				
				≥90nmol/L	251	224	1.17	0.93, 1.48				
				30-nmol/L increase	NR	NR	1.13	1.02, 1.25				
				<30nmol/L	49	63	0.80	0.52, 1.23				

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
	Prostate Cancer (Winter/Spring)			30–49nmol/L	304	286	1.09	0.86, 1.40		
				50–69nmol/L	288	297	1.00	Reference		
				70–89nmol/L	145	128	1.14	0.85, 1.53		
				≥90nmol/L	38	50	0.74	0.46, 1.18		
				30-nmol/L increase	NR	NR	0.97	0.83, 1.14		
	Prostate Cancer (Summer/Autumn)			<30nmol/L	13	14	0.97	0.45, 2.10		
				30–49nmol/L	132	172	0.87	0.66, 1.16		
				50–69nmol/L	296	329	1.00	Reference		
				70–89nmol/L	297	259	1.34	1.05, 1.71		
				≥90nmol/L	180	144	1.46	1.07, 2.00		
				30-nmol/L increase	NR	NR	1.25	1.08, 1.45		

*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.

Table 26a. Vitamin D and breast cancer: Characteristics of nested case control studies (updated from original report)

Table 2a: Vitamin D and Breast Cancer Characteristics of Nested Case-Control Studies (adapted from original report)						Confounders/Effect Modifiers Adjusted						
Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons		Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Comments
Radioreceptor Assay and Radioimmunoassay												
Bertone-Johnson 2005 ¹⁴² NHS US (38° 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	
Radioimmunoassay												
Freedman 2008 ¹⁴³ PLCO Trial US (38° 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	
NEW Studies Chemiluminescence Assay												
Neuhouser 2012 ¹²⁴ WHI US (various)	• Health status • Mean age (SD), y	Post-menopausal 65.1 (SD 6.8)				X	X	X			X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset
Engel, 2010 ¹³⁸ French E3N France	• Health outcome • Mean age (SD), y	nd 56.9 (6.4)			Breast cancer risks: Quintile 1 vs. Quintile 2, 3		X	X				
McCullough, 2009 ¹³⁶ Cancer Prevention Study-II (CPS-II)	• Health outcome • Mean age (SD), y	nd 69.6 (5.8)			Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X		

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Enzyme-linked Immunoabsorption Assay										
Kuhn 2013 ¹⁴⁵ EPIC Multiple Countries	<ul style="list-style-type: none">Health outcomeMean age (SD), y	Nd 50.7 (SD 8.8)	Breast Cancer risks: Quintile 1 vs Quintile 2, 3, 4, 5		X	X		X	X	This analysis does not include data from the Malmo site, as these data were analyzed and published separately as Almquist, 2010, reference 126 in the original report.
HPLC-Tandem Mass Spectrometry										
Almquist, 2010 ¹³⁷ Malmo Diet and Cancer Study	<ul style="list-style-type: none">Health outcomeMean age (SD), y	Healthy 57 (SD 7.3)	Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Rejnmark, 2009 ¹³⁹ Denmark	<ul style="list-style-type: none">Health outcomeMean age (SD), y	nd 58 (29–87)	Breast cancer risks: Tertile 1 vs. Tertile 2, 3							

Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioimmunoassay										
Freedman 2007 ¹⁰³ NHANES III US (38° N) [17971526]	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y	Non-institutionalized 44 (ND)	Breast cancer risks: Quintile 1 vs. Quintile 2	X	X	X		X	X	
Eliassen, 2011 ¹³⁵ NHSIII	<ul style="list-style-type: none">• Health outcome• Mean age (SD), y• Male (%)	nd 44.9 (SD 4.4) 0%	Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Chemiluminescence Assay										
Jacobs, 2011 ¹⁴⁴ Women's Healthy Eating and Living (WHEL) US (various)	<ul style="list-style-type: none">• Health outcome• Mean age (SD), y• Male (%)	Cancer in remission 51.9 (SD 9) 0%	Breast cancer risks: Quartile 4 vs. Quartile 1, 2, 3							This article contains both prospective cohort and case-control data. Case-control data given here
Ordonez-Mena 2013 ⁹⁷ ESTHER Saarland, Germany	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	nd NR (50–74) 54%	Breast cancer risk: Tertile 2 vs Tertile 1 and 3		X	X			X	confounders—add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

Table 27a. Vitamin D and breast cancer: Results of nested case control studies (updated from original report)

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				
Radioreceptor Assay and Radioimmunoassay															
Bertone-Johnson 2005 ¹⁴²	Pre- and Post- menopausal	Breast cancer (701/1425)	<1-82 mo	25(OH)D	≤50 (1 st batch)	159	297	1	Reference	nd	B				
NHS [16103450]					≤70 (2 nd batch)										
					≤45 (3 rd batch)										
					51-70	149	278	0.95	0.66, 1.36						
					72-85										
					47 to 60										
					72-82	125	266	0.74	0.51, 1.06						
					87-97										
					62-72										
					85-97	144	296	0.8	0.58, 1.11						
					100-117										
					75-90										
					≥100	124	265	0.73	0.49, 1.07						
					≥120										
					≥92										
Breast cancer <60 y (701/1425)						97	191	1	Reference	NS					
						84	170	0.96	0.62, 1.49						
						77	164	0.8	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						

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
Radioimmunoassay											
Freedman 2008 ¹⁴³ 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		
Chemiluminescence Assay											
Neuhouser 2012 ¹²⁴ WHI	50-79 years	Breast Cancer (1080 cases, 1080 controls)	NR	25(OH)D	<36.7	105	181	1.06	0.78, 1.43	0.60	A
					36.7 to <50.9	68	147	1.11	0.83, 1.49		
					50.9 to <64.9	84	162	0.99	0.75, 1.31		
					>64.9	53	130	1.00	Reference		
Engel 2010 ¹³⁸ French E3N	born between 1925 and 1950	Breast Cancer (636 cases, 1272 controls)	≤10 years	25(OH)D	<49.5 nmol/L	226	630	OR=1.00	Reference	0.02	A
					49.5-67.5 nmol/L	198	600	0.81	0.63, 1.04		
					>67.5 nmol/L	191	603	0.73	0.55, 0.96		
McCullough 2009 ¹³⁶ Cancer Prevention Study-II (CPS-II)	47-85 years	Breast Cancer(516 cases, 516 controls)	1month-6.9 years	25(OH)D	<36.7	89	193	OR=1.00	Reference	0.60	A
					36.7–49.7	115	217	1.29	0.86, 1.94		
					49.8-60.7	99	204	1.14	0.75, 1.72		
					60.8-73.1	118	220	1.44	0.96, 2.18		
					>73.1	95	198	1.09	0.70, 1.68		
Enzyme-linked Immunoabsorption Assay											
Kuhn 2013 ¹⁴⁵	40-65 years	Breast Cancer#	4.1 yrs	25(OH)D	Q1: ≤39.3	342	688	1.00	Reference	0.67	A
EPIC					Q2: 39.4-50.9	357	707	1.03	0.83, 1.29		
					Q3: 51.0-63.0	324	670	0.94	0.74, 1.19		
					Q4: >63.0	368	717	1.07	0.85, 1.36		
					log2 (continuous)	1391	2782	1.01	0.86, 1.19		
HPLC-Tandem Mass Spectrometry											
Almquist 2010 ¹³⁷ Malmo Diet and Cancer	Born 1923-1950	Breast Cancer (213 cases, 213	7.0 years	25(OH)D3	Quartile 1(<70l)	NR	213	OR=1.00	Reference		
					Quartile 2 (71-86)	NR	164	0.84	0.60,1.15		

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
Study [HPLC only]		controls)	7.0 years	25(OH)D2+D3	Quartile 3(87-105)	NR	176	0.84	0.60, 1.17	0.71	A
					Quartile 4(>105)	NR	192	0.93	0.66,1.33		
					Quartile 1(72)	NR	191	1.00	Reference		
					Quartile 2 (72-87)	NR	170	0.95	0.68, 1.31		
					Quartile 3(88-106)	NR	183	0.94	0.68, 1.32		
					Quartile 4(>106)	NR	191	0.96	0.68, 1.37		
Rejnmark 2009 ¹³⁹	Pre- and Post- menopausal	Breast Cancer(142 cases, 420 controls)	NR	25(OH)D	<60nmol/L	NR	NR	1.00	Reference	<0.05	B
					60-84nmol/L	NR	NR	0.94	0.59, 1.47		
					>84nmol/L	NR	NR	0.52	0.32, 0.85		
	Premenopausal				<60nmol/L	NR	NR	1.00	Reference		
					60-84nmol/L	NR	NR	0.59	0.26, 1.33		
					>84nmol/L	NR	NR	0.38	0.15, 0.97		
	Postmenopausal				<60nmol/L	NR	NR	1.00	Reference		
					60-84nmol/L	NR	NR	1.20	0.67, 2.16		
					>84nmol/L	NR	NR	0.71	0.38, 1.30		

*Correlation between two assays evaluated for 20 women: For all samples, the Pearson correlation coefficient between assays was 0.36 (P = 0.12); after the exclusion of two outliers, the correlation was 0.73 (P = 0.0005)

#Total number of women not reported

Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report)

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
Radioimmunoassay											
Freedman 2007 ¹⁰³ 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*		
Eliassen 2011 ¹³⁵ NHSIII		Breast Cancer (613 cases, 1218 controls)	NR	25(OH)D	Quartile 1(<46 nmol/L)	141	441	1.00	Reference	0.320	A
					Quartile 2(46.0 to 61.5 nmol/L)	151	456	1.05	0.79, 1.39		
					Quartile 3(61.5 to <76.5 nmol/L)	145	452	0.95	0.71, 1.29		
					Quartile 4 (≥76.5 nmol/L)	176	482	1.20	0.88, 1.63		
Chemiluminescence Assay											
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living (WHEL)		Breast Cancer (512/3085)	NR	25(OH)D	<25 nmol/L(deficient)	nr	51	OR=1.14	0.57, 2.31	0.85	B
					≥25and <50 nmol/L(insufficient)	nr	282	1.00	0.68, 1.48		
					≥50 and <75 nmol/L(suboptimal)	nr	410	1.05	0.76, 1.47		
					≥75 nmol/L(optimal)	nr	281	1.00	Reference		
		Premenopausal			<25 nmol/L(deficient)	nr	6	0.17	0.01, 4.56	0.61	
					≥25and <50 nmol/L(insufficient)	nr	31	1.02	0.33, 3.16		
					≥50 and <75 nmol/L(suboptimal)	nr	45	1.76	0.64, 4.87		
					≥75 nmol/L(optimal)	nr	36	1.00	Reference		
		Postmenopausal			<25 nmol/L(deficient)	nr	37	1.45	0.62,3.37	0.49	
					≥25and <50 nmol/L(insufficient)	nr	202	1.09	0.68, 1.76		
					≥50 and <75 nmol/L(suboptimal)	nr	266	0.90	0.60, 1.36		
					≥75 nmol/L(optimal)	nr	187	1.00	Reference		
Ordonez-Mena 2013 ⁹⁷ ESTHER	50-74 years	Breast Cancer	8 yrs	25(OH)D	Q1	38	1464	1.08	0.72, 1.60		B
					Q2+Q3	71	2951	1.00	Reference		
					Q4	26	846	1.39	0.89, 2.18		

^A Total number of women not reported.

Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies (updated from original report)

Author Year Trial/Cohort Country (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	
Radioimmunoassay												
Stolzenberg-Solomon 2006 ¹⁴⁷ ATBC Finland (60°N) [17047087]	Health status	All smokers	Assay	RIA (DiaSorin)	Exocrine pancreatic risk stratified by baseline 25(OH)D quintiles	X	X			X	X	
	Mean age (range/SD), y	58										
	Male (%)	100	Season blood drawn	nd; but result adjusted for this variable								
Stolzenberg-Solomon 2009 ¹⁴⁸ PLCO US (various) [19208842]	Health status	DM: 10.5%	Assay	RIA (Heartland Assays lab)	Pancreatic risk stratified by baseline 25(OH)D quintiles		X	X		X	X	
	Mean age (range), y	66 (55-74)										
	Male (%)	65.2	Season blood drawn	All seasons	Pancreatic risk stratified by residential sun exposure levels and baseline 25(OH)D quartiles							
Chemiluminescence Assay												
Stolzenberg-Solomon, 2010 ¹⁴⁶ Cohort Consortium Vitamin D Pooling Project or Rarer Cancers	Health status	nd			Pancreatic risk stratified by baseline 25(OH)D sextiles							
	Mean age (SD), y	nd (nd)										
	Male (%)	66.5%										
Afzal 2013 ⁹⁹ Denmark	Health status Mean age (SD), y Male (%)	NR 58 (47-65) 45%			Pancreatic risk stratified by baseline 25(OH)D category		X	X			X	HR (95%CI) for pancreatic cancer are shown in Figure 1

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report)

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
Radioimmunoassay										
Stolzenberg-Solomon 2006 ¹⁴⁷ 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	1.3	0.70, 2.40		
				41.1-51.1	47	80	2.12	1.15, 3.90*		
				51.1-65.5	35	81	1.5	0.81, 2.76		
				>65.5	57	79	2.92	1.56, 5.48*		
Stolzenberg-Solomon 2009 ¹⁴⁸ 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		
Chemiluminescence Assay										
Stolzenberg-Solomon 2010 ¹⁴⁶ Cohort Consortium Vitamin D Pooling Project or Rarer Cancers		Pancreatic Cancer (952 cases, 1333 controls)	nd	<25	115	256	1.00	Reference	0.14	A
				25 to <37.5	164	389	1.04	0.74, 1.44		
				37.5 to <50.0	208	494	1.10	0.79, 1.55		
				50.0 to <75.0	306	764	1.06	0.76, 1.48		
				75.0 to <100.0	120	310	1.08	0.73, 1.59		
				>100	39	69	2.24	1.22, 4.12		

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
Afzal 2013 ⁹⁹		Pancreatic Cancer	28 yrs	25(OH)D, 50% reduction in plasma levels	109	9791	HR 1.05	0.84, 1.30		B

* Statistically significant (P<0.05)

Table 30c. Vitamin D and immunologic outcomes: Characteristics of Infectious Disease Continuous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioreceptor assay										
Li-Ng, 2009 ¹⁵⁰ US Long Island, NY	<ul style="list-style-type: none">• Health status• Mean age (range/SD), y• Male (%)	nd 58.1 (SD 13.4) 20.3%	Duration of Upper Respiratory Tract stratified by 25(OH)D levels							
Enzyme-linked Immunoabsorption Assay										
Laaksi, 2010 ¹⁵¹ Pori Brigade, Finland	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy Nd (nd) 100%	Days absent from duty stratified by 25(OH)D ₃ levels		X					

Table 30d. Vitamin D and immunologic outcomes: Characteristics of Infectious Disease Dichotomous RCTs (updated from original report)

Report Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioreceptor assay										
Li-Ng, 2009 ¹⁵⁰	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 58.1 (SD 13.4) 20.3%	Upper respiratory tract stratified by 25(OH)D medians							
Radioimmunoassay										
Goldring 2013 ¹⁶¹ UK	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	NR 3 44%	Wheeze ever and lower respiratory tract infection stratified by 25(OH)D medians	X	X				X	Children of mothers enrolled in a 3-arm RCT of vitamin D administration were prospectively followed
Chemiluminescence assay										
Manaseki-Holland, 2012 ¹⁴⁹ Kabul, Afghanistan	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd nd (nd) 52%	Pneumonia stratified by 25(OH)D ₃ medians							Age groups reported but not mean age, only father's ethnicity reported
Enzyme-linked Immunoabsorption Assay										
Laaksi, 2010 ¹⁵¹ Pori Brigade, Finland	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy Nd (nd) 100%	Days absent from duty stratified by 25(OH)D ₃ levels		X					
HPLC Tandem Mass Spectrometry										
Murdoch, 2012 ¹⁵² VIDARIS New Zealand	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)• Mean age (SD), y• Male (%)	nd 48 (10) 25% 10.4 (2.4) 55%	Days of missed work per episode stratified by 25(OH)D ₃ and Placebo medians							

Table 31c. Vitamin D and immunologic outcomes: Results of Infectious Disease RCTs-Continuous Outcomes (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. Analyzed	Final mean	Final SD	Net Diff	Net Diff 95% CI	Study Quality
Radioreceptor assay										
Li-Ng 2009 ¹⁵⁰	18-80 years	Duration of Upper Respiratory Tract	12 wks	Vit D 2000IU/day	78	5.4	4.8	+1.0	-1.2, 1.4	B
				Placebo	70	5.3	3.1	Reference		
Enzyme-linked Immunoabsorption Assay										
Laaksi 2010 ¹⁵¹	18-28 years	Days absent from duty	6 mos	Vit D3 400 IU	80	2.2	3.2	-0.8	-1.9, 0.3	B
				Placebo	84	3.0	4.0	Reference		

Table 31d. Vitamin D and immunologic outcomes: Results of Infectious Disease RCTs-Dichotomous Outcomes (updated from original report)

Report	Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
	Radioreceptor assay											
	Li-Ng 2009 ¹⁵⁰	18-80 years	Upper Respiratory Tract	12 weeks	Vit D	2000IU/day	28	78	OR 0.79	0.41, 1.54	0.61	B
						Placebo	29	70	1	Reference		
	Radioimmunoassay											
	Goldring 2013 ¹⁶¹		wheeze ever			either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	11	56	OR 0.56	0.20, 1.57	0.27	
				3 yrs	Vit D	control	14	50	OR 1.00	Reference		A
			lower respiratory tract infection			either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	14	54	OR 1.00	0.35, 2.91	1	

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Chemiluminescence assay											
Manaseki- Holland 2012 ¹⁴⁹	infants aged 1-11 months	All Pneumonia First episode	NR	Vit D3	100,000IU	260	1782 person years	IRR =1.065	0.895, 1.268	0.476	A
					Placebo	2445	1782 person years	1	Reference		
		All Pneumonia repeat episode			100,000IU	138	2031 person years	IRR =1.685	1.282, 2.212	<0.000 1	
					Placebo	82	2027 person years	1	Reference		
Enzyme-linked immunoabsorption assay											
Laaksi 2010 ¹⁵¹	18-28 years	Self-reported common cold symptoms	6 months	Vit D3	400 IU	45	80	OR 1.17	0.63, 2.16	0.619	B
				Placebo	Placebo	44	84	1	Reference		
		No days absent from duty		Vit D3	400 IU	41	80	1.89	1.01, 3.54	0.045	
				Placebo	Placebo	30	84	1	Reference		
HPLC Tandem Mass Spectrometry											
Murdoch 2012 ¹⁵² VIDARIS	18 yrs & older	No. of URTs per person*	18 months	Vit D3 & Placebo	100,000IU	3.7	161	RR =0.97	0.85,1.11	0.65	A
					Placebo	3.7	161	1	Reference		
	No. of days if missed work per episode	100,000IU			0.76	161	RR 1.03	0.81, 1.30	0.82		
		Placebo			0.76	161	RR 1	Reference			
		Duration of symptoms			100,000IU	12	161	RR 0.96	0.73, 1.25	0.76	
					Placebo	12	161	RR 1	Reference		
					control	11	50	OR 1.00	Reference		

*Included in Table 31d (dichotomous outcomes) because differences reported as relative risks

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report)

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 ¹⁷⁹ PEPPS ^A US (41°N) [17535985]	<ul style="list-style-type: none"> • Health status • Age range, y • Male (%) 	Healthy 20-29 0%	<ul style="list-style-type: none"> • Assay method • Season blood drawn 	ELISA ND Comparison of mean 25(OH)D levels in cases and controls		x	x			
Radioimmunoassay										
Shand, 2010 ¹⁷⁷ EMMA Vancouver, Canada	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd 0%		Preeclampsia stratified by 25(OH)D medians	X	X	X		X	X
Chemiluminescence Assay										
Wei, 2012 ¹⁷⁴ International Trial of Antioxidants in the Prevention of Preeclampsia (INTAPP) Canada	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of preeclampsia 30.3 (4.8) 0%		Preeclampsia stratified by 25(OH)D tertiles		X	X	X	X	X
Wei 2013 ¹⁷² INTAPP Canada	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 28.68 (SD 5.44) 0%		Preeclampsia stratified by 25(OH)D medians		X	X		X	X
Enzyme-linked immunoabsorption assay										
Bodnar 2007 ¹⁷⁹ PEPPS ^A US (41°N) [17535985]	<ul style="list-style-type: none"> • Health status • Age range, y • Male (%) 	Healthy 20-29 0%	<ul style="list-style-type: none"> • Assay method • Season blood drawn 	ELISA ND Comparison of mean 25(OH)D levels in cases and controls		x	x			

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
HPLC-Tandem mass Spectrometry										
Baker, 2010 ¹⁷⁵ US Chapel Hill, NC	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	Healthy 28 (23-34) 0%		Severe preeclampsia stratified by 25(OH)D tertiles		X	X		X	
Powe, 2010 ¹⁷⁸ US Boston, MA	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	nd 30.4 (SD 6) 0%		Severe preeclampsia stratified by 25(OH)D quartiles		X			X	
Scholl 2013 ¹⁷³ Camden Study Camden, New Jersey US	<ul style="list-style-type: none">• Health status• Mean age (SD), y• Male (%)	Healthy/NR 22.8 (SD 5.4) 0%		Preeclampsia stratified by 25(OH)D quartiles	X	X	X			X
Woodham 2011 ¹⁷⁶ Chapel Hill, UK	<ul style="list-style-type: none">• Health status• Mean age (range), y• Male (%)	nd 29 (25-33) 0%		Severe preeclampsia stratified by 25(OH)D		X	X		X	

^A Pregnancy Exposures and Preeclampsia Prevention Study

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report)

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
Radioimmunoassay										
Shand 2010 ¹⁷⁷		preeclampsia	10-20 weeks gestation	25(OH)D	<37.5	10	NR	0.91	0.31, 2.62	A
					≥37.5	18	NR	1.00	Reference	
					<50	17	NR	1.39	0.54, 3.53	
					≥50	11	NR	1.00	Reference	
					<75	21	NR	0.57	0.19, 1.66	
					≥75	6	NR	1.00	Reference	
Chemiluminescence Assay										
Wei 2012 ¹⁷⁴		preeclampsia	12-18 weeks gestation	25(OH)D	per SD increase	32	697	0.79	0.52, 1.20	A
					<50	15	272	1.24	0.58, 2.67	
					>50	17	425	1.00	Reference	
			24-26 weeks gestation		per SD increase	28	604	0.68	0.44, 1.05	
					<50	19	236	3.24	1.37, 7.69	
					>50	9	368	1.00	Reference	
Wei 2013 ¹⁷² INTAPP		preeclampsia	24-26 weeks gestation	25(OH)D	<50 nmol/L	NR	NR	2.97	1.23, 7.20	B
					≥50 nmol/L			1.00	Reference	
Enzyme-linked immunoabsorption assay										
Bodnar 2007 ^{179A} 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	1.7, 14.1	B
HPLC-Tandem mass Spectrometry										
Baker 2010 ¹⁷⁵	Pregnant or lactating women	severe preeclampsia	NR	25(OH)D	< 50	22	160	5.41	2.02, 14.52	B
					50-74.9	10	51	2.16	0.85, 5.40	
					≥75	11	30	1.00	Reference	

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
Powe 2010 ¹⁷⁸		severe preeclampsia	NR	25(OH)D	Quartile 1 (ND)	39 (overall)	170 (overall)	1.50	0.57, 3.96	B
					Quartile 2 (ND)			1.04	0.39, 2.76	
					Quartile 3 (ND)			0.67	0.23, 1.91	
					Quartile 4 (ND)			1.00	Reference	
Scholl 2013 ¹⁷³		preeclampsia	20 weeks gestation	25(OH)D	<30	12	121	2.13	1.07, 4.26	B
					30-40	12	116	2.09	1.04, 4.22	
					40-50	7	154	0.94	0.41, 2.17	
					>=50	38	750	1.00	Reference	
Woodham 2011 ¹⁷⁶		severe preeclampsia	NR	25(OH)D		41	164	0.95	0.94, 0.97	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.

Table 35d. Vitamin D and Bone Health: Characteristics of Observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioimmunoassay						
Cauley, 2008 ¹⁹⁵ WHI-OS nd	<ul style="list-style-type: none"> • Health status • Mean age (Range), y • Male (%) 	Post-menopausal Nd (50-79) 0%	Serum 25(OH)D controls: 59.60 ± 18.05 nmol/l cases: 55.95 ± 20.28 nmol/l	Quartile 1: 9.2-47.5 nmol/L vs. Quartile 2: 47.6-70.6 nmol/L vs. Quartile 3: 60.2-70.6 nmol/L vs. Quartile 4: 70.7-121.5 nmol/L vs. per 2.5 nmol/L decrease vs. per 25 nmol/L decrease	nd	
Barbour, 2012 ¹⁹⁴ US Pittsburgh, PA and Memphis, TN	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd nd nd	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532–995) 719 (517–978) 716 (501– 940) Supplemental calcium intake (% yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (% yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes, any non-spine fracture no/yes	Quartile 1: ≤44.5 nmol/l vs. Quartile 2: 44.5-60.9 nmol/L vs. Quartile 3: 60.9-79.9 nmol/L vs. Quartile 4: >79.9 nmol/L	nd	
Burgi 2011 ²⁰³ US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y 	nd 19.5 (SD 1.8)	nd	3.8-49.3 nmol/L vs. 49.3-66.5 nmol/L vs.	nd	

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
	<ul style="list-style-type: none"> • Male (%) 	0%			66.5-82.0 nmol/L vs. 82.0-99.5 nmol/L vs. 99.5-281.3 nmol/L
Cauley 2011 ¹⁹⁹ WHI OS US	<ul style="list-style-type: none"> • Health status • Mean age (Range), y • Male (%) 	nd 64 (50-70) nd	nd		<50 nmol/L vs. 50-<75 nmol/L vs. ≥75 nmol/L
Looker 2013 ¹⁹⁶ NHANES III US (multiple cities)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 75.2 25.7%	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L		3 categories per 1 SD unit decline in serum 25OHD
Chemiluminescence Assay					
Rouzi 2012 ²⁰⁰ Jeddah, Saudi Arabia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 61.3 (SD 7.2) nd	Serum 25(OH)D: 34.27±22.80 nmol/L		<17.90 nmol/L vs. >45.1 nmol/L
Menant, 2012 ¹⁹³ Sydney, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 78 (SD 4.6) Range: 70-90 46%	serum vitamin D- 62.2±24.6 nmol/L		≤ 50nmol/l Vs. > 50nmol/l
Michael, 2011 ¹⁸⁹ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 70.3 (SD 3.7) Range: 50-79 0%	Serum vitamin D- 48.2+/-21.4 nmol/L		≥ 75 nmol/l Vs. 50-74nmol/l Vs. 25-49 nmol/l Vs. ≤ 25 nmol/l

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
HPLC Tandem Mass Spectrometry						
Barrett-Connor, 2012 ¹⁹⁸ US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy, Overweight/Obese, and diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12% 74 (SD 6) 100%	nd	Normal level Vs. Low vit D	nd	
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	nd 74.6 (SD 4.6) 30%	Serum vitamin D: 66.2+/-25.8 nmol/L	Normal level Vs. Low level (season specific, ranges 43-61 nmol/L)	nd	
Holvik 2013 ¹⁹⁷ Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	46.1-59.2% good or very good health 71.9 (SD 3.9) 28%	median (25th and 75th percentiles) s-25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L	Quartile 1: 4.5-42.1 vs. Quartile 2: 42.2-53.5 vs. Quartile 3: 53.5-67.8 vs. Quartile 4: 67.9-250.0	nd	

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Radioimmunoassay												
Cauley, 2008 ¹⁹⁵ WHI-OS nd		hip fractures	1°	7.1 yrs	Quartile 1: 9.2-47.5 nmol/L	NR	244	OR	1.71	1.05, 2.79	0.015	A
					Quartile 2: 47.6-70.6 nmol/L	NR	195		1.09	0.70, 1.71		
					Quartile 3: 60.2-70.6 nmol/L	NR	167		0.82	0.51, 1.31		
					Quartile 4: 70.7-121.5 nmol/L	NR	193		1.00	Reference		
					per 2.5 nmol/L decrease	NR	799		1.03	1.01, 1.05		
					per 25 nmol/L decrease	NR	799		1.33	1.06, 1.68		
Barbour, 2012 ¹⁹⁴ US Pittsburgh, PA and Memphis, TN	age 70-79	Hip fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	84	2501	HR	1.92	0.97, 3.83	0.217	B
					Quartile 2: 44.5-60.9 nmol/L				0.75	0.32, 1.72		
					Quartile 3: 60.9-79.9 nmol/l				1.86	1.00, 3.45		
					Quartile 4: >79.9 nmol/l				1.00	Reference		
		nonspine fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	247	2494	HR	1.21	0.83, 1.75	0.752	
					Quartile 2: 44.5-60.9 nmol/L				1.01	0.68, 1.49		
					Quartile 3: 60.9-79.9 nmol/l				1.12	0.78, 1.60		
					Quartile 4: >79.9 nmol/l				1.00	Reference		
Burgi 2011 ²⁰³ US	9-50 yrs	stress fracture	1°	NR	3.75-49.25 nmol/L	600	1200	OR	1.00	Reference	0.02	B
					49.5-66.5 nmol/L				0.77	0.54, 1.11		
					66.8-82 nmol/L				0.76	0.52, 1.10		
					82.3-99.5 nmol/L				0.61	0.42, 0.91		
					99.75-281.25 nmol/L				0.51	0.34, 0.78		
Cauley 2011 ¹⁹⁹ WHI OS US	Post- menop ausal women	fractures	1°	8.6 yrs	<50 nmol/L	150	270	OR	1.00	Reference	0.02	A
					50- <75 nmol/L	156	321		0.82	0.58, 1.16		
					≥75 nmol/L	84	189		0.56	0.35, 0.90		
					<50 nmol/L	241	508	OR	1.00	Reference	0.043	
					50- <75 nmol/L	108	193		1.48	1.05, 2.10		
					≥75 nmol/L	30	57		1.33	0.73, 2.43		
					<50 nmol/L	89	182	OR	1.00	Reference	0.72	
					50- <75 nmol/L	71	140		1.02	0.69, 1.79		
					≥75 nmol/L	31	60		1.09	0.50, 2.37		

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality	
Asians					<50 nmol/L	37	80	OR	1.00	Reference	0.22		
					50- <75 nmol/L	45	85		1.49	0.76, 2.93			
					≥75 nmol/L	30	59		1.66	0.68, 4.02			
					<50 nmol/L	29	55	OR	1.00	Reference	0.29		
					50- <75 nmol/L	9	18		0.64	0.15, 2.79			
					≥75 nmol/L	6	15		0.43	0.09, 2.08			
Looker 2013 ¹⁹⁶ NHANES III	major osteoporotic fracture	1°	7 yrs	per 1 SD unit decline in serum 25OHD	400	4749	RR	1.27	1.12, 1.44		A		
					212	NR		1.14	0.97, 1.34				
					188	NR		1.40	1.13, 1.74				
Chemiluminescence Assay													
Rouzi, 2012 ²⁰⁰ Jeddah, Saudi Arabia		fragility fractures	1°	5.2 yrs	<17.90 nmol/L	138	707	OR	1.25	0.91, 1.70		A	
					>45.1 nmol/L				1.00	Reference			
Menant, 2012 ¹⁹³ Sydney, Australia		Primary— Falls in men	1°	1 y	≤ 50nmol/l	94	215	IRR	1.93	1.19, 3.15	0.008	B	
					> 50nmol/l			IRR	1.00	Reference			
		Primary— Falls in women			≤ 50nmol/l	115	248	IRR	0.83	0.56, 1.23			0.362
					> 50nmol/l			IRR	1.00	Reference			
Michael, 2011 ¹⁸⁹ US (various)		Primary— Physical performanc e summary score	1°	6 y	≥ 75 nmol/l	NR	64	RR	3.66	1.88, 5.45	<0.001	A	
					50-74nmol/l	NR	148	RR	2.32	0.89, 3.75			
					25-49 nmol/l	NR	255	RR	1.64	0.28, 3.01			
					≤ 25 nmol/l	NR	67	RR	1	Reference			
HPLC Tandem Mass Spectrometry													
Barrett-Connor, 2012 ¹⁹⁸ US (various)	51-70 yrs; ≥71 yrs	nonspine fracture	1°	4.6 yrs	Normal level	100	594	HR	1.2	0.8, 1.8		A	
					Low vit D	34	183		1.00	Reference			
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)		Hip fracture	1°	11 yrs	Normal level	118	1126	HR	1.00	Reference	NR	A	
					Low level (season specific, ranges 43-61 nmol/L)	72	495		1.34	0.97, 1.84			

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Holvik 2013 ¹⁹⁷ Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)		hip fracture	1°	10.7 yrs	Q1: 4.5-42.1	317	256	HR	1.34	1.05, 1.70		A
					Q2: 42.2-53.5	294	255		1.13	0.90, 1.44		
					Q3: 53.5-67.8	272	255		1.10	0.87, 1.39		
					Q4: 67.9-250.0	279	256		1.00	Reference		

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Radioreceptor Assay											
Pilz 2009 ⁷³ Hoorn Study Netherlands	<ul style="list-style-type: none">• Health status• Mean Age (range), y• Male (%)	More than 20% Type 2 Diabetes or impaired glucose tolerance 69.2 (6.5) 50%			All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Visser 2006 ²²² Longitudinal Aging Study Netherlands (52°N) [16960177]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	General population ^B >65 51	<ul style="list-style-type: none">• Assay method• Season blood drawn	Competitive protein binding ND	Comparison of various 25(OH)D concentration categories		X	X			X
Radioimmunoassay											
Jia 2007 ²¹⁹ UK (57°N) [17442130]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Not terminally ill or demented >75 52	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA ND	Comparison of various 25(OH)D concentration categories		X		X	X	X
Sambrook 2004 & 2006 ^{220,221} FREE ^A Australia (33°S) [15531500 & 16598375]	<ul style="list-style-type: none">• Health status• Age range, y• Male (%)	Not bedridden >65 22	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Dia-sorin) ND	Association with log 25(OH)D		X		X		
Melamed 2008 ⁸⁵ NHANES III US (various) [18695076]	<ul style="list-style-type: none">• Health status• Age mean (range), y• Male (%)	General population 45 (≥20) 46	<ul style="list-style-type: none">• Assay method• Season blood drawn	RIA (Dia-sorin) ND	Comparison of various 25(OH)D concentration categories	X	X	X	X	X	X

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Bolland 2010 ⁵⁸ New Zealand	<ul style="list-style-type: none"> • Health status • Age range, y • Male (%) 	Healthy Post-menopausal 74 (SD 4.2) 0%	Comparison of various 25(OH)D concentration categories		X	X	X		X
Johansson 2012 ²¹¹ MrOS Sweden: Gothenburg, Malmö, Uppsala	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Some with diabetes, htn, cancer, stroke, MI, angina 75.7 (SD 3.4) 100%	Death and mortality stratified by varying 25(OH)D concentration levels		X		X		X
Kritchevsky 2012 ²¹² Health, Aging, and Body Composition (ABC) Study US Pittsburgh, Memphis	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Well-functioning 74.7 (SD 2.9) 49%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Semba 2010 ⁹³ InCHIANTI Italy	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	Nd 78 (72-85) 67.3%	All-cause mortality and cardiovascular mortality stratified by 25(OH)D quartiles		X	X		X	X
Smit 2012 ²¹³ NHANES III US (various)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Malnourished/frailty, pre-frail, not frail 69.4 (SD 0.3) 46.5%	All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Szulc 2009 ²¹⁴ MINOS Study Montceau les Mines, France	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 64 (SD 7) 55%	Mortality stratified by 25(OH)D quartiles	X	X	X	X		X
Szulc 2009 ²¹⁵ MINOS Study Montceau les Mines, France	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 64 (SD 7) 100%	Mortality stratified by 25(OH)D quartiles		X	X	X		X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Tomson 2013 ⁷⁵ Whitehall study London, UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%		Death (all non-vascular) and Death (all causes) stratified by 25(OH)D doubling concentration			X	X		X
Sempos 2013 ²¹⁸ NHANES III US	<ul style="list-style-type: none"> • Health status • Mean age (SE), y • Male (%) 	NR 45 (SE 0.47) 49%		All-cause mortality stratified by 25(OH)D in 9 categories		X			X	
Formiga 2014 ⁷⁷ Octabaix Spain	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Oldest old 85 (SD 0) 39.4%		Total mortality stratified by 25(OH)D quartiles		X		X		
Chemiluminescence Assay										
Eaton 2011 ⁷⁰ WHI substudy US (multisite)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 65.1 (SD 7.6) 0%		Post-menopausal women 50-79 years stratified by 25(OH)D quartiles			X	X	X	X
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living Well (WHEL) Study	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Cancer in remission 51.9 (SD 9) 0%		Breast cancer survivors stratified by 25(OH)D concentration categories						
Skaaby 2013 ⁸⁶ Monica10 and Inter99 Denmark	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR Monica 10: 55.4 Inter 99: 46.1 Monica 10: 50.2 Inter 99: 49.2		All-cause mortality stratified by 25(OH)D quartiles		X		X	X	X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Wong 2013 ²¹⁷ Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 76 (70-88) 100%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X		X
Schottker 2013 ⁷⁶ ESTHER Germany	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	NR 62 (SD 6.5) 43.8%		All-cause mortality stratified by 25(OH)D tertiles	X	X		X	X	X
Signorello 2013 ⁷⁴ Southern Community Cohort Study US	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) • Male (%) 	nd nd nd 100%		All-cause mortality stratified by 25(OH)D quartiles			X			X
Enzyme-linked Immunoabsorption Assay										
Hutchinson 2010 ⁷⁹ Tromsø Study Tromsø, Norway	<ul style="list-style-type: none"> • Health status • Mean Age (range), y • Male (%) 	Nd nd nd		Smoking and non-smoking cause of death stratified by 25(OH)D quartiles		X	X	X		X
Fedirko 2012 ¹⁰¹ EPIC US (4 sites)	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	nd 62.1 (4.2) 40.5%		Diagnosis at age of 62 stratified by 25(OH)D quintiles		X	X	X	X	X
Lin 2012 ⁸³ General Population Trial of Linxian, China	<ul style="list-style-type: none"> • Health status • Mean Age (SD), y • Male (%) 	Healthy, Hypertension 56.5 (7.9) 55%		All-cause mortality stratified by continuous 25(OH)D		X	X	X		X

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
HPLC-Tandem Mass Spectrometry									
Cawthon 2010 ⁹⁸ MrOS (multisite) US	<ul style="list-style-type: none">• Health status• Mean age (Age range), y• Male (%)	>80% Excellent/good health status 74 (> or =65) nd	Association with log 25(OH)D	X	X	X	X	X	X
Michaelsson 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	<ul style="list-style-type: none">• Health status• Mean Age (range), y• Male (%)	More than 1/3 being treated for hypertension 71 (0.6) 100%	Overall mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Kestenbaum 2011 ⁸¹ Cardiovascular Health Study US (various)	<ul style="list-style-type: none">• Health status• Mean Age (range), y• Male (%)	nd 73 (SD 4) 42%	All-cause mortality stratified by 25(OH)D quartiles						
Virtanen 2011 ²¹⁶ Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	<ul style="list-style-type: none">• Health status• Mean Age (range), y• Male (%)	Post-menopausal, 54-62% hypertension 61.8 (53.4-72.7/SD 6.2) 48.6%	Overall mortality stratified by 25(OH)D tertiles		X	X	X		X
Welsh 2012 ⁶⁰ MIDSPAN Family Study Renfrew and Paisley, UK	<ul style="list-style-type: none">• Health status• Mean Age (range), y• Male (%)	vitamin D not deficient 45.2 (6.2) 46%	All-cause mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	<ul style="list-style-type: none">• Health status• Mean Age (SD), y• Male (%)	nd 74 (SD 4.6) 30%	Comparison of various 25(OH)D concentration categories		X	X	X		X

^AFracture Risk Epidemiology in the Elderly

^B~40% with CVD and ~60% arthritis

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report)

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
Radioreceptor Assay											
Pilz 2009 ⁷³ Hoorn Study Netherlands	Men and women (50-75 yrs)	all-cause mortality	6.2 yrs	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	21	152	HR=1.97	1.08, 3.58	0.027	B
					2nd-4th quartiles (mean 25(OH)D 45.6-78.9)	30	462	1.00	Reference		
Visser 2006 ²²² 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	0.72, 1.40		
					50-74.9	30	440	0.91	0.65, 1.26		
					≥75	29	231	1	Reference		
Radioimmunoassay											
Jia 2007 ²¹⁹ 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	1.4	0.73, 2.70		
					30.1-37.0 (M)/ 24.1-30.2 (F)	21	80	0.9	0.45, 1.79		
					37.1-47.0 (M)/ 30.3-39.0 (F)	17	78	0.8	0.39, 1.62		
					47.1-82.0 (M)/ 39.1-82.0 (F)	16	79	1	Reference		
Sambrook 2004 & 2006 ^{220,221} 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
Melamed 2008 ⁸⁵ 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	Reference		
	>20, men only	Mortality	104	25(OH)D	<17.8	nd	nd	1.04	0.83, 1.30	nd	C

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												
	>20, women only	Mortality	104	25(OH)D	17.8-24.3	nd	nd	0.94	0.75, 1.19	nd	C												
					24.4-32.1	nd	nd	0.82	0.64, 1.05														
					>32.1	nd	nd	1	Reference														
					<17.8	nd	nd	1.55	1.15, 1.98														
					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	Reference														
					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	Reference								
									≥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	Reference																			
Bolland 2010 ⁵⁸ New Zealand	Post-menopausal women	Primary— Death	5 yrs	25(OH)D						<50 nmol/L	13				373			HR=0.90	0.4, 2.0	0.82	A		
										≥50 nmol/L	16				366			1.00	Reference				
Johansson 2012 ²¹¹ MrOS (Sweden)	Men (70-81 yrs)	death	8.2 yrs	25(OH)D						per SD decrease	577				2878			HR=1.16	1.06, 1.26	NR	A		
Kritchevsky 2012 ²¹² Health, Aging, and Body Composition (ABC) Study	Older community dwelling men and women (70-79 yrs)	all-cause mortality	8.5 yrs	25(OH)D						< 25 nmol/L	44				108			HR=2.27	1.59, 3.24	<0.001	B		
					25 to <50 nmol/L	241	750	1.48		1.20, 1.84													
					50 to <75 nmol/L	229	931	1.25		1.02, 1.52													
					≥75 nmol/L	177	849	1.00		Reference													
		all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	10	25	2.02		1.02, 3.99	0.001												
					25 to <50 nmol/L	82	279	1.54	1.16, 2.06														
					50 to <75 nmol/L	138	620	1.22	0.96, 1.55														
					≥75 nmol/L	143	691	1.00	Reference														
	whites	all-cause mortality	8.5 yrs	25(OH)D	<25 nmol/L	34	83	2.59	1.57, 4.26	<0.001													
					25 to <50 nmol/L	159	471	1.76	1.20, 2.57														
					50 to <75 nmol/L	91	311	1.60	1.07, 2.39														

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
Semba 2010 ⁹³ InCHIANTI Italy		all-cause mortality	6.5 yrs	25(OH)D	≥75 nmol/L	34	158	1.00	Reference		
					1st quartile: <26.3 nmol/L	NR	252	HR 2.11	1.22, 3.64		
					2nd quartile: 26.3-40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.3-64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		
Smit 2012 ²¹³ NHANES III	Adults (60 and over)	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	2.98	2.01, 4.42		A
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	2.37	1.44, 3.89		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	2.50	1.48, 4.21		
					Quartile 4: >84.1 nmol/l	NR	NR	1.43	0.83, 2.46		
	pre-frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.97	1.61, 2.40		
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	1.62	1.29, 2.03		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	1.51	1.16, 1.97		
					Quartile 4: >84.1 nmol/l	NR	NR	1.82	1.41, 2.35		
	not frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.25	0.97, 1.60		
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	1.20	0.96, 1.49		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	1.11	0.88, 1.40		
					Quartile 4: >84.1 nmol/l	NR	NR	1.00	Reference		
Szulc 2009 ²¹⁴ MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	per SD decrease	600	782	1.22	1.01, 1.48		A
					Quartile 1 <65 nmol/l summer or <40 nmol/l other months	NR	NR	1.44	1.03, 2.03		
					Quartiles 2-4	NR	NR	1.00	Reference		
Szulc 2009 ²¹⁵ MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	Quartile 1	NR	NR	1.6-1.8	NR	<0.05	A
					Quartiles 2-4	NR	NR	1.00	Reference		
Tomson 2013 ⁷⁵		Death,	13.1 yrs	25(OH)D	Doubling Concentration	1857	5409	0.77	0.69, 0.86		B

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
Whitehall study		all non-vascular Death, all causes				3215	5409	0.78	0.72, 0.85		
Sempos 2013 ²¹⁸ NHANES III		death from all-cause	15 yrs	25(OH)D	<20 20-29 30-39 40-49 50-59 60-74 75-99 100-119 ≥120	79 297 592 694 668 775 533 110 36	251 1270 2340 2790 2526 3046 2156 518 202	1.6 1.5 1.3 1.1 1.2 1.1 1.0 1.1 1.4	1.2, 2.2 1.2, 1.8 1.1, 1.5 0.96, 1.3 1.01, 1.30 0.99, 1.30 Reference 0.9, 1.4 0.9, 2.2		A
Formiga 2014 ⁷⁷ Octabaix		total mortality	2.8 yrs	25(OH)D	Q1: <34.94 Q2: 34.94-61.65 Q3: 61.66-83.37 Q4: >83.37	15 18 11 14	71 77 84 80	1.28 1.36 0.76 1.00	0.61, 2.6 0.67, 2.74 0.34, 1.68 Reference	0.41	B
Chemiluminescence Assay											
Eaton 2011 ⁷⁰ WHI substudy US (multisite)	Post-menopausal women 50-79 years	all-cause mortality	10 yrs	25(OH)D	Quartile 1: 3.25-36.50 nmol/L Quartile 2: 36.51-49.95 nmol/L Quartile 3: 49.96-65.38 nmol/L Quartile 4: 65.39-146.67 nmol/L		608 606 608 607	HR=1.25 1.13 1.17 1.00	0.80-1.95 0.73-1.75 0.75-1.81 Reference	0.39	A
Jacobs 2011 ¹⁴⁴ Women's Healthy Eating and Living Well (WHEL) Study	Breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 years	mortality	7.3 yrs	25(OH)D	Insufficient, <50 nmol/L Sufficient, ≥50 nmol/L	164 336		1.13 1.00	0.72, 1.79 Reference	0.59	B
Skaaby 2013 ⁸⁶ Monica10 and Inter99		all-cause mortality	10 yrs	25(OH)D	per 10nmol/L Q1 Q2 Q3	633	8329	0.95 1.00 0.79 0.81	0.92, 0.99 Reference 0.64, 0.98 0.65, 1.01	0.005 0.041	B

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
					Q4			0.73	0.57, 0.92		
Wong 2013 ³¹⁷					per 10nmol/L decrease in 25(OH)D			1.04	1.01, 1.07		
					halving of 25(OH)D			1.21	1.08, 1.35		
					Q1: 10-52.8	1144	4203	1.20	1.02, 1.42		
					Q2: 52.9-67.3			1.00	Reference		
					Q3: 67.4-81.6			0.99	0.84, 1.17		
					Q4: 81.7-238.4			0.99	0.83, 1.17		
Schottker 2013 ⁷⁶ ESTHER					<30	238	1444	1.68	1.41, 2.01		
					30-50	448	4199	1.17	1.01, 1.35		
					>50	397	3935	1.00	Reference		
					<30	142	609	1.41	1.13, 1.77		
					30-50	269	1706	1.09	0.90, 1.31		
					>50	236	1394	1.00	Reference		
					<30	238	835	2.08	1.58, 2.76		
					30-50	448	2493	1.30	1.04, 1.63		
					>50	397	2541	1.00	Reference		
Signorello 2013 ⁷⁴ Southern Community Cohort Study US					Quartile 4: (>54.1nmol/L)	364	827	1.00	Reference	<0.001	A
					Quartile 3: (37.9-54.1 nmol/L)	405	868	1.17	0.95, 1.45		
					Quartile 2: (25.5-37.9 nmol/L)	482	945	1.41	1.14, 1.74		
					Quartile 1: <25.5 nmol/L)	601	1064	1.80	1.43, 2.27		
					Quartile 4: (>54.1nmol/L)	181	400	1.00	Reference	0.003	
					Quartile 3: (37.9-54.1 nmol/L)	266	565	1.15	0.87, 1.53		
					Quartile 2: (25.5- 37.9nmol/L)	353	730	1.19	0.91, 1.57		
					Quartile 1: <25.5 nmol/L)	475	855	1.60	1.20, 2.14		
					Quartile 4: (>54.1nmol/L)	179	419	1.00	Reference	<0.001	
					Quartile 3: (37.9-54.1 nmol/L)	136	296	1.09	0.78, 1.52		
					Quartile 2: (25.5-37.9 nmol/ L)	129	214	1.99	1.37, 2.90		
					Quartile 1: <25.5 nmol/L)	122	203	2.11	1.39, 3.21		

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
Enzyme-linked Immunoabsorption Assay											
Hutchinson 2010 ⁷⁹ Tromsø Study (Norway) nonsmokers	Men(55-74 yrs) Women (50-74 yrs)	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	247	1184	HR=1.32	1.07-1.62	NR	B
					Quartile 2: mean=46.7 (sd=6.0)	198	1187	1.06	0.86-1.31		
					Quartile 3: mean=56.2 (sd=6.0)	190	1192	1.09	0.88-1.34		
					Quartile 4: mean=72.3 (sd=13.2)	163	1188	1.00	Reference		
	smokers	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	156	597	1.06	0.83-1.35	NR	
					Quartile 2: mean=46.7 (sd=6.0)	143	606	0.97	0.76-1.25		
					Quartile 3: mean=56.2 (sd=6.0)	138	607	1.04	0.81-1.33		
					Quartile 4: mean=72.3 (sd=13.2)	124	600	1.00	Reference		
Fedirko 2012 ¹⁰¹ EPIC US (4 sites)	Men and women (diagnosed at an average age of 62)	overall mortality	73 mos	25(OH)D	<36.3	128	242	HR=1.00	Reference	<0.01	B
					36.4-48.6	108	239	0.82	0.63, 1.07		
					48.7-60.5	117	241	0.91	0.70, 1.18		
					60.6-76.8	95	240	0.78	0.59, 1.03		
					>76.8	93	240	0.67	0.50, 0.88		
						793	1101	HR=1.01	0.97, 1.05		
Lin 2012 ⁸³ General Population Trial of Linxian (China)	Men 40-69 yrs	all-cause mortality	24 yrs	25(OH)D	continuous 25(OH)D	479	608	0.99	0.94, 1.04	0.7	B
	Women 40-69 yrs					314	493	1.03	0.97, 1.10	0.348	
	HPLC-Tandem Mass Spectrometry										
Cawthon 2010 ⁹⁸ MrOS (multisite) US	Men (51-70 yrs; ≥71 years)	all-cause mortality	7.3 yrs	25(OH)D	Quartile 1: <49.75 nmol/L		372	HR=0.95	0.68, 1.34	0.961	B
					Quartile 2: ≥49.75 to <63.0 nmol/L		370	1.05	0.75, 1.47		
					Quartile 3: ≥63.0 to <75.0 nmol/L		372	0.89	0.64, 1.24		

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
					Quartile 4: ≥ 75.0		376	1.00	Reference	0.706	
					Deficient, < 50 nmol/L		376	0.94	0.67, 1.32		
					Insufficient, 50 to < 75 nmol/L		737	0.97	0.72, 1.30		
					Sufficient, ≥ 75 nmol/L		377	1.00	Reference		
					per SD decrease			1.01	0.89, 1.14		
Michaelsson 2010 ⁸⁴ Uppsala Longitudinal Study of Adult Men Uppsala (Sweden)	Elderly men birth 1920-1924	overall mortality	12.7 yrs	25(OH)D	< 10 th percentile (< 46 nmol/L)	76	119	HR=1.43	1.11, 1.84		B
					10th-90th percentile (46-93 nmol/L)	444	956	1.00	Reference		
					> 90 th percentile (> 93 nmol/L)	64	119	1.27	0.97, 1.66		
Kestenbaum 2011 ⁸¹ Cardiovascular Health Study	> 65 years	Primary— all-cause mortality	14 yrs	25(OH)D	> 75 nmol/L	329	681	HR=1.00	Reference	0.012	B
					37.5-75.0 nmol/L	668	1247	1.15	1.00, 1.33		
					< 37.5 nmol/L	229	384	1.29	1.05, 1.57		
					continuous per 25 nmol/L	1226	2312	1.09	1.02, 1.17		
Virtanen 2011 ²¹⁶ [HPLC alone] Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	Men (average age 61.8)	mortality	9.1 yrs	25(OH)D	Tertile 1: 8.9-34.0 nmol/L	39	379	2.06	1.12, 3.80	0.02	A
					Tertile 2: 34.1-50.8 nmol/L	31	378	1.68	0.92, 3.07		
					Tertile 3: 50.9-112.8 nmol/L	17	379	1.00	Reference		
Welsh 2012 ⁶⁰ MIDSPAN Family Study Scotland	Men and women	Primary— all-cause mortality	14.4 yrs	25(OH)D	per 1 SD increase	70	1492	0.74	0.56, 0.99		B
					Deficient, < 37.5 nmol/L	NR	689	2.02	1.17, 3.51		
					Not deficient ≥ 37.5 nmol/L	NR	803	1.00	Reference		
de Boer 2012 ⁸⁷ Cardiovascular Health Study US (various)	White older adults	Death	11 yrs	25(OH)D	Normal level	539	1126	HR=1.00	Reference	NR	A
					Low level (season specific, ranges 43-61 nmol/L)	287	495	1.32	1.14, 1.53		

^AFracture Risk Epidemiology in the Elderly

^BPer unit change in the log-transformed concentration

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
SYSTOLIC BLOOD PRESSURE						
Radioreceptor assay						
Scragg 1995 ²³⁷ Cambridge, UK (52°N) [7498100]	<ul style="list-style-type: none"> • 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
Radioimmunoassay						
Pfeifer 2001 ²³⁸ Lower Saxony, Germany (52°N) [11297596]	<ul style="list-style-type: none"> • 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 ⁹⁶ New Delhi, India (28.5°N) [19125756]	<ul style="list-style-type: none"> • 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
DIASTOLIC BLOOD PRESSURE						
Radioreceptor assay						
Scragg 1995 ²³⁷ Cambridge, UK (52°N) [7498100]	<ul style="list-style-type: none"> • 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
Radioimmunoassay						
Pfeifer 2001 ²³⁸ Lower Saxony, Germany (52°N) [11297596]	<ul style="list-style-type: none"> • 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 ⁹⁶ New Delhi, India	<ul style="list-style-type: none"> • Health status 	Healthy, obese	25(OH)D: 36.5 nmol/L (treatment group), 30.0	Vit D ₃ 120,000 IU every 2 weeks vs.	100% (implied); supervised home visits	Excluded subjects who refused

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
(28.5°N) [19125756]	<ul style="list-style-type: none"> • Mean age (SD), y • Male (%) 	44 (8) 100%	nmol/L (control group)	Placebo		subsequent blood draws
NEW Studies						
Radioimmunoassay						
Forman 2013 ²²⁷ Boston, MA	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 51 (44-59) 34.6%	Serum vitamin D- 39.3 (26.8-83.5 IQR) nmol/L	Vit D ₃ 100,000 IU/day Vs. Vit D ₃ 2000 IU/day Vs. Vit D ₃ 4000 IU/day Vs. placebo	96.6%	
Jorde 2010 ²³⁰ Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Using blood pressure or lipid lowering medication Overweight/Obese 47.5 (SD 11.4) 35.8%	58.0 ± 21.1 nmol/L	DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day Vs. DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day Vs. PP (placebo)+500 mg calcium/day	Vitamin D/placebo capsules 95%-DD group, 96%-DP group and 96%-PP group calcium tablets 82%, 84% and 83%, respectively.	
Enzyme-linked Immunoabsorption Assay						
Salehpour 2012 ²³⁴ Tehran, Iran	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight, obese 38 (SD 8.1) 0%	Serum 25(OH)D Vit D group: 36.8 +/- 30 nmol/l Placebo group - 46.9 +/- 32 nmol/l	Vit D 25 µg/day Vs. placebo	nd	
Witham 2013 ²³⁵ UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 39.4 (SD 11.8) 0%	<50 nmol/L	Vit d3 100,000 units Vs. placebo	nd	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Toxqui 2013 ²²⁸ Spain	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 26.5 (SD 3.8) 0%	Serum: D-placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L	vit d 200 IU/day Vs. placebo	>96%	
HPLC-tandem mass spectrometry						
Gepner 2012 ²²⁹ Madison, WI	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy Postmenopausal 63.9 (SD 3) 0%	Serum vitamin D- 78.3+/- 26.5 nmol/L	Placebo Vs. Vit D ₃ 2500 IU/day	nd	
Wood 2012 ²³¹ Aberdeen, UK	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy Post-menopausal 63.9 (SD 2.3) 0%	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l	400 IU Vit D/day Vs. placebo	nd	
Wamberg 2013 ²³⁶	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight/obese 41.2 (18-50) (SD 6.8) 27%	34.6±10.3 nmol/L	7000 IU cholecalciferol vs. placebo	94±8%	
Not reported						
Zhu 2013 ²³² Shanghai, China	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 20.3 (SD 0.8) 14.3%	Habitual Ca intake CaD group - 426.5 +/- 152.2 mg/d Control group - 392.1 +/- 141.1 mg/d	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day Vs. energy-restricted diet alone (control)	95.8% in the calcium+D group	
Daly 2009 ²³³ Melbourne, Australia	<ul style="list-style-type: none"> • Health status • Mean age (SD), y 	Healthy, obese 61.2 (SD 7.5)	Serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit	85 ± 21%	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
	• Male (%)	100%	nmol/l	D)/day Vs. control (no additional fortified milk) (400 ml reduced fact milk fortified with 1000 mg clacium+800 IU Vit D)/day Vs. control (no additional fortified milk)		

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/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Radioreceptor assay														
Scragg 1995 ²³⁷ UK [7498100]	63-76 y, Both	SBP	1°	5 wk	Vit D ₃ 100,000 IU (2.5 mg), 1 dose Placebo	95 94	mm Hg	149 147	-5 -5	-14.4, 4.4 ^A -17.9, 7.9 ^A	0	-4.2, 4.2 ^A	0.81	A
Radioimmunoassay														
Pfeifer 2001 ²³⁸ Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D ₃ 800 IU +Ca carbonate 1200 mg Ca carbonate 1200 mg	73 72	mm Hg	144.1 140.6	-13.1 -5.7	nd nd	- 7.4	-13.6, -1. 2 ^A	0.02	B
Nagpal 2009 ⁹⁶ New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D ₃ 120,000 IU every 2 wk Placebo	35 36	mm Hg	124 124	0.6 -3.4	-2.7, 3.9 -5.8, -1.0	4	-0.02, 8.0	0.06	B
DIASTOLIC BLOOD PRESSURE														
Radioreceptor assay														
Scragg 1995 ²³⁷ UK [7498100]	63-76 y, Both	DBP	1°	5 wk	Vit D ₃ 100,000 IU (2.5 mg), 1 dose Placebo	95 94	mm Hg	82 82	-1 -1	-6.8, 4.8 ^A -6.8, 4.8 ^A	0	-2.8, 2.8 ^A	0.92	A
Radioimmunoassay														
Pfeifer 2001 ²³⁸ Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D ₃ 800 IU +Ca carbonate 1200 mg Ca carbonate 1200 mg	73 72	mm Hg	84.7 82.6	-7.2 6.9	nd nd	- 0.3	-0.7, -0.1 _A	0.1	B
Nagpal 2009 ⁹⁶ New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D ₃ 120,000 IU every 2 wk Placebo	35 36	mm Hg	78 77	0.4 -1.3	-2.1, 3.0 -3.2, 0.7	1.7	-1.5, 4.9	0.31	B

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality						
NEW Studies																				
Radioimmunoassay																				
Forman 2013 ²²⁷ Boston, MA	19-50 yrs	DBP	1°	3 months	Vit D ₃ 1000 IU/day	68	mm Hg	79.8	final= 78.0	se=1.6 ^B	-0.9	-5.7, 3.9	0.71	A						
					Vit D ₃ 2000 IU/day	73		77.6	final= 76.0	se=1.8 ^B	-2.9	-7.9, 2.1	0.26							
					Vit D ₃ 4000 IU/day	70		79.8	final= 78.0	se=1.6 ^B	-0.9	-5.7, 3.9	0.71							
					placebo	72		78	final= 78.9	se=1.8 ^B										
		SBP			Vit D ₃ 1000 IU/day	68		124.7	final= 122.5	se=2.0 ^B	-2.4	-8.6, 3.8	0.45							
					Vit D ₃ 2000 IU/day	73		122.8	final= 120.0	se=2.4 ^B	-4.9	-11.6, 1.8	0.15							
					Vit D ₃ 4000 IU/day	70		130.4	final= 126.6	se=2.6 ^B	+1.7	-5.3, 8.7	0.63							
					placebo	72		122.2	final= 124.9	se=2.4 ^B										
					Jorde 2010 ²³⁰ Norway															
					19-50, 51-70 yrs	DBP		1°	1 yr	DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	114	mm Hg	76.5		change= 1.0	sd=7.4	+0.8	-1.3, 2.9	0.45	B
(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	104	74.9	change= 1.0	sd=8.3			+0.8			-1.4, 3.0	0.48									
DBP	(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	112	74.8	change= 0.2		sd=8.3														
	SBP	(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	114	124		change= 1.2	sd=11.4			+2.3	-0.9, 5.5		0.15							
SBP	(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	104	121	change= 3.5		sd=11.8	+4.6			1.3, 7.9	<0.00 1									
	SBP	(placebo)+500 mg calcium/day DD (40,000 IU Vit D ₃ /week)+500 mg calcium/day DP (20,000 IU Vit D ₃ /week)+500 mg calcium/day PP	112	125		change= -1.1	sd=12.8													

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Enzyme-linked Immunoabsorption Assay														
Salehpour 2012 ²³⁴ Tehran, Iran	19-50 yrs (pre- menopause)	DBP	1°	12 weeks	Vit D 25 µg/day	42	mm Hg	67.9	final= 70.2	sd=8.8	-1.9	-6.1, 2.3	0.37	B
		DBP			placebo	43		71.9	final= 72.1	sd=10.6				
		SBP			Vit D 25 µg/day	42		110.5	final=111	sd=11.3	-3.4	-8.7, 1.9	0.20	
		SBP			placebo	43		116.7	final= 114.4	sd=13				
Witham 2013 ²³⁵	≥18 yrs (women)	SBP	2°	8 weeks	Vit d3 100,000 units	25	mm Hg	119	change= 2.0	sd=7.9	+3.0	-1.9, 8.0	0.22	A
		SBP			placebo	25		122	change= -1.0	sd=9.1				
		DBP			Vit d3 100,000 units	25		78	change= -0.1	sd=5.7	+0.6	-2.5, 3.7	0.70	
		DBP			placebo	25		78	change= -0.7	sd=5.2				
Toxqui 2013 ²²⁸	18-35 yrs (women)	SBP	2°	16 weeks	vit d 200 IU/day	55	mm Hg	109.3	final= 105.9	sd=9.1	-2.4	-5.9, 1.1	0.178	B
		SBP			placebo	54		107.7	final= 108.3	sd=9.4				
		DBP			vit d 200 IU/day	55		67.1	final= 66.6	sd=7.3	-0.1	-2.9, 2.7	0.944	
		DBP			placebo	54		69.2	final= 66.7	sd=7.5				
HPLC-tandem mass spectrometry														
Gepner 2012 ²²⁹ Madison, WI	Post- menopause	brachial DBP	2°	4 months	placebo	57	mm Hg	72.6	change= -0.4	sd=4.4				A
		brachial DBP			Vit D ₃ 2500 IU/day	57		72.45	change= -0.7	sd=5.1	-0.3	-2.1, 1.5	0.73	
		brachial SBP			placebo	57		122.2	change= -2.5	sd=10.9				
		brachial SBP			Vit D ₃ 2500 IU/day	57		122.3	change= -0.3	sd=8.4	+2.2	-1.4, 5.8	0.23	
		central DBP			placebo	57		73.7	change= -0.5	sd=4.4				
		central DBP			Vit D ₃ 2500 IU/day	57		73.5	change= -0.7	sd=5.1	-0.2	-2.0, 1.6	0.82	
		central SBP			placebo	57		115.6	change= -2.1	sd=9.7				
		central SBP			Vit D ₃ 2500 IU/day	57		116.7	change= -0.3	sd=7.0	+1.8	-1.3, 4.9	0.26	

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Wood 2012 ²³¹ Aberdeen, UK	Post- menopause	DBP	1°	1 yr	400 IU Vit D/day	97	mm Hg	77.68	change= -2.5	-3.6, -1.4	-0.4	-1.9, 1.1	0.60	A
		placebo			100	77.7		change= -2.1						
		SBP			400 IU Vit D/day	96		128.16	change= -2.2	-3.3, -0.7	+0.2	-2.2, 2.6	0.87	
		SBP			placebo	98		128.18	change= -2.4					
Wamberg 2013 ²³⁶	18-50 yrs	SBP	1°	26 weeks	7000 IU cholecalciferol	22	mm Hg	135	final=129	sd=13	-2	-11, 7	0.65	A
		placebo			21	132		final=131	sd=16					
		DBP			7000 IU cholecalciferol	22		85	final=84	sd=11	0	-7, 7	1	
		DBP			placebo	21		81	final=84	sd=11				
Not reported														
Zhu 2013 ²³² Shanghai, China	19-50 yrs	DBP	1°	12 weeks	(energy- restricted diet+600 mg calcium+125 IU Vit D)/day	22	mm Hg	70.7	final= 64.2	sd=4.7	-1.2	-4.6, 2.2	0.48	B
		energy- restricted diet alone (control)			21	70		final= 65.4	sd=6.3					
		SBP			(energy- restricted diet+600 mg calcium+125 IU Vit D)/day	22		119.2	final= 109.6	sd=9.9	-2.3	-8.6, 4.0	0.46	
		SBP			energy- restricted diet alone (control)	21		123	final= 111.9	sd=10.4				
Daly 2009 ²³³ Melbourne, Australia	51-70 yrs	DBP	1°	2 yr	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day	66	mm Hg	69.5	change= 4.2	2.1, 6.2	+0.3	-2.6, 3.2	0.84	A
		control (no additional fortified milk)			58	71		change= 3.9						
		SBP			(400 ml reduced fact milk fortified with 1000 mg clacium+800 IU	66		123.7	change= 6.8	4.2, 9.3	+1.5	-2.4, 5.4	0.45	

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					Vit D)/day									
		SBP			control (no additional fortified milk)	58		120.4	change= 5.3	2.4, 8.2				

^aEstimated from available data

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor Assay						
Zhu 2008 ²⁴⁷ Perth, Australia (32 °S) [18410225]	<ul style="list-style-type: none"> • 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)	
El-Hajj 2006 ⁴⁸ Beirut, Lebanon (33°53'N) [16278262]	<ul style="list-style-type: none"> • 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)	
Radioimmunoassay						
Jorde 2010 ²⁴³ nd	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Overweight/Obese 50.8 (10.7) nd	57.7 +/-20.7 nmol/L	DD (Vit D ₃ 40,000 IU/week+500 mg calcium Vs.) DP (Vit D ₃ 20,000 IU/week+500 mg calcium) Vs. PP (Placebo+500 mg calcium)	Vitamin D- DD-95%, DP-96%, PP-96%, calcium-82%, 84%, and 83%	
Khadiilkar 2010 ²⁴⁰ Pune, India	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd 14.6 (14.3-15.3) 0%	Vit D + Ca- 24.5 nmol/L (12.7-33.2) Placebo +Ca- 20.8 nmol/L (12.7-30.4)	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day Vs. Placebo x 4 times/year + 250 mg elemental calcium/day	nd	
Holmlund-Suila 2012 ²³⁹ Helsinki, Finland	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	nd Birth 50%	53 nmol/L	Vit D ₃ 1600 IU/day Vs. Vit D ₃ 1200 IU/day Vs. Vit D ₃ 400 IU/day	82% compliance	.

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Nieves 2012 ²⁴⁴ New York, US	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Vit D deficient/depleted 61.2 (SD 7.6) 0%	Serum 25(OH)D: 29.0±14.3 nmol/L	1,000 IU Vit D ₃ Vs. placebo	95%	
Chemiluminescence Assay						
Iuliano-Burns 2012 ²⁴² Australian Antarctic Division	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 41 (24-65) 83%	Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose-63+/-12 nmol/L	monthly (Vit D ₃ 50,000 IU/month) vs. bimonthly (Vit D ₃ 50,000 IU in alternate months) vs. single dose (one does of Vit D ₃ 50,000 IU pre departure)		
HPLC-Tandem Mass Spectroscopy						
Andersen 2008 ²⁴⁶ Copenhagen, Denmark (55 N°) [18208636]	<ul style="list-style-type: none"> • 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.
Grimnes 2012 ²⁴¹ Norway	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Post-menopausal 63.5 (SD 6.8) 0%	Serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L	high dose (6500 IU/day)+1000 mg elemental calcium/day vs. standard dose(800 IU/day)+1000 mg elemental calcium/day	97% compliance	
Molgaard 2010 ²⁴⁸ Copenhagen and	<ul style="list-style-type: none"> • Health status 	Healthy	Vitamin D intake: pacebo-2.6±1.4ug/d	10 µg Vit D ₃ /day Vs.	placebo:88±12 5ug/d: 90±10	

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Frederiksberg, Denmark	<ul style="list-style-type: none"> • Mean age (SD), y • Male (%) 	11.4 (SD 0.2) 0%	Serum vitamin D level:placebo-43.4±17.1 nmol/L Calcium intake: placebo-955±588 mg/d	5 µg Vit D ₃ /day Vs. placebo	10ug/d 88±11	
Macdonald 2013 ²⁴⁵ Scotland, UK	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) • Health status • Mean age (SD), y • Male (%) 	Healthy, post menopausal 64.6 (SD 2.3) 0%	35.8±16.4 nmol/L	Vit D3 400 IU vs. Vit D3 1000 IU vs. placebo	92% (range 72% to 98%)	

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

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Radioreceptor Assay														
Zhu 2008 ²⁴⁷ Perth, Australia (32 °S) [18410225]	71+. Women only	Hip BMD	1°	12	Vit D ₂ 1000 IU + Ca citrate 1200 mg	123	mg/c m ²	851	0.50%	-0.09, 1.09	0.30%	nd	NS	A
					Ca citrate 1200 mg	133		826	0.20%	-0.19, 0.59				
El-Hajj 2006 ⁴⁸ Beirut, Lebanon (33°N) [16278262]	10-17 y girls	BMC	1°	12	Vit D 2000 IU	55	kg	1.2	6.20%	4.7, 7.7	0.10%	-1.1, 2.0 ^C	NS	C
					Vit D 200 IU	58		1.1	6.10%	4.6, 7.6	1.10%	-0.8, 3.2 ^C	NS	
					Placebo	55		1.1	5.00%	3.8, 6.2				
	Subgroup – Premenar chal girls, mean age 10 y	BMC	1°	12	Vit D 2000 IU	14	kg	0.8	11.60%	9.4, 13.8	4.20%	0.7, 7.7 ^C	NS	
					Vit D 200 IU	12		0.7	11.40%	9.1, 13.7	4.00%	0.5, 7.5 ^C	NS	
					Placebo	8		0.8	7.40%	4.7, 10.1				
Radioimmunoassay														
Jorde 2010 ²⁴³ nd	19-50, 51- 70 yrs	BMD L2- L4	1°	1 yr	DD (Vit D ₃ 40,000 IU/week+500 mg calcium)	110	g/cm ²	1.27	change= 0.008	sd=0.036	+0.00	-0.01, 0.01	0.85	
					DP (Vit D ₃ 20,000 IU/week+500 mg calcium)	97		1.235	change= 0.008	sd=0.039	+0.01	0.0, 0.01	0.86	
					PP (Placebo+500 mg calcium)	105		1.251	change= 0.007	sd=0.042				B
		BMD total hip			DD (Vit D ₃ 40,000 IU/week+500 mg calcium)	110		1.107	change= 0.008	sd=0.014	-0.00	-0.01, 0.0	0.64	
					DP (Vit D ₃ 20,000 IU/week+500 mg calcium)	97		1.067	change= 0.011	sd=0.014	+0.0	-0.0, 0.01	0.36	
					PP (Placebo+500 mg calcium)	105		1.092	change= 0.009	sd=0.017				
Khadiolkar 2010 ²⁴⁰ Pune, India	9-18 yrs	L2-L4 bone mineral apparent density	1°	1 yr	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g/cm ³	NR	change= 4.2	0.6, 9.3	+0.5	NC	NC	B
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g/cm ³	NR	change= 3.7	1.0, 7.7				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality				
Holmlund-Suila 2012 ²³⁹ Helsinki, Finland	0-6 mos	L2-L4 BMC	2°	10 week (age of 3 months)	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g	NR	change= 10.5	4.6, 17.2	-0.8	NC	NC	A				
		Placebo x 4 times/year + 250 mg elemental calcium/day			24	g	NR	change= 11.3	5.4, 18.0									
		cortical bone density			Vit D ₃ 1600 IU/day	29	g/cm ³	NR	final=716	se=7	-8	-12.1, -3.9	<0.00 1					
	total and trabecular bone density	Vit D ₃ 1200 IU/day			28		NR	final=726	se=7	+2	-2.1, 6.1	0.34						
		Vit D ₃ 400 IU/day			25		NR	final=724	se=8									
		Vit D ₃ 1600 IU/day			29		NR	final=430	se=12	-18	-25, -11	<0.00 1						
		Vit D ₃ 1200 IU/day			28		NR	final=451	se=12	+3	-4, 10	0.39						
		Vit D ₃ 400 IU/day			25		NR	final=448	se=13									
		Nieves 2012 ²⁴⁴ New York, US			Postmeno- pause	femoral neck BMD	1°	2 yr	1,000 IU Vit D ₃	55	g/cm ²	NR	change=- 0.2		NR	+0.6	NC	NC
placebo	48			NR					change=- 0.8	NR								
spine BMD	1,000 IU Vit D ₃		55			1.154			change=- 0.5	NR	+0.1	NC	NC					
	placebo		48			1.212			change=- 0.6	NR								
total hip BMD	1,000 IU Vit D ₃		55			1.043			change=- 0.5	NR	+0.2	NC	NC					
	placebo		48			1.04			change=- 0.7	NR								
trochanter BMD	1,000 IU Vit D ₃		55			NR			change=- 0.3	NR	+0.15	NC	NC					
	placebo		48			NR			change= -0.45	NR								
Chemiluminescence Assay																		
Iuliano-Burns 2012 ²⁴² Australian Antarctic Division	19-50, 0- 70 yrs	Femoral neck BMD	1°	up to 12 months (end of expedition)		monthly (Vit D ₃ 50,000 IU/month)			36	g/cm ²	0.86	final= 0.85	sd=0.13	-0.06	-0.12, 0	0.06	B	
					bimonthly (Vit D ₃ 50,000 IU in alternate months)	35		0.82	final= 0.82	sd=0.10	-0.09	-0.15, - 0.03	<0.00 1					
					single dose (one dose of Vit D ₃ 50,000 IU pre departure)	31		0.9	final= 0.91	sd=0.13								

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		Lumbar spine (L1- L4) BMD			monthly (Vit D ₃ 50,000 IU/month)	36		1	final= 0.98	sd=0.16	-0.09	-0.17, - 0.01	0.03	
					bimonthly (Vit D ₃ 50,000 IU in alternate months)	35		1	final= 1.00	sd=0.09	-0.07	-0.14, -0.0	0.05	
					single dose (one dose of Vit D ₃ 50,000 IU pre departure)	31		1.08	final= 1.07	sd=0.18				
		monthly (Vit D ₃ 50,000 IU/month)			36		1.02	final= 0.85	sd=0.13	-0.23	-0.30, - 0.16	<0.00 1		
		bimonthly (Vit D ₃ 50,000 IU in alternate months)			35		1.01	final= 1.01	sd=0.08	-0.07	-0.13, - 0.01	0.02		
		single dose (one dose of Vit D ₃ 50,000 IU pre departure)			31		1.08	final= 1.08	sd=0.15					
	Total proximal femur BMD	Vit D ₂ 300,000 IU x 4 times/year + 250 mg elemental calcium/day			25	g	NR	change= 10.1	6.1, 14.7	+1.9	NC	NC		
		Placebo x 4 times/year + 250 mg elemental calcium/day			24	g	NR	change= 8.2	4.9, 12.6					
		HPLC-Tandem Mass Spectroscopy												
Andersen 2008 ²⁴⁶ Copenhagen, Denmark (55 N°) [18208636]	18-53, Women only	Lumbar spine BMD	1°	12	Vit D ₃ 400	30/21 ^A	mg/c m 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 ²⁴⁶ Copenhagen, Denmark (55 N°) [18208636]	18-64, Men only	Lumbar spine BMD	1°	12	Vit D ₃ 400	25/19 ^A	mg/c m 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 ²⁴⁶ 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	7-Sep		1.5	10%	nd	-5%	nd	NS	
					Placebo	7-Aug		1.7	15%	nd				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Grimnes 2012 ²⁴¹ Norway	Postmeno- pause	Total hip BMD	1°	1 yr	high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.79	change= 0.31	sd=1.59	-0.25	-0.63, 0.13	0.19	A
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.791	change= 0.56	sd=1.70				
		Femoral neck BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.758	change= 0.03	sd=2.08	-0.14	-0.59, 0.31	0.86	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.757	change= 0.17	sd=1.87				
		L2-L4 BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	0.901	change= 0.25	sd=3.19	-0.07	-0.80, 0.66	0.85	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	0.902	change= 0.32	sd=3.23				
		Total Body BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm ²	1	change= 0.18	sd=1.14	-0.02	-0.29, 0.25	0.88	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm ²	1.002	change= 0.20	sd=1.23				
Molgaard 2010 ²⁴⁸ Copenhagen and Frederiksberg, Denmark	9-18 yrs	L1-L4 BMC	1°	12 months	10 µg Vit D ₃ /day	74	g	28.9	final=36. 3	sd=8.6	-1.2	-4.3, 1.9	0.44	B
					5 µg Vit D ₃ /day	73	g	29.4	final=37. 6	sd=10.3	+0.1	-3.2, 3.4	0.95	
					placebo	74	g	29.2	final=37. 5	sd=10.2				
		L1-L4 BMD			10 µg Vit D ₃ /day	74	g/cm ²	0.695	final=0.7 80	sd=0.113	-0.01	-0.05, 0.03	0.68	
					5 µg Vit D ₃ /day	73	g/cm ²	0.698	final=0.7 86	sd=0.115	-0.0	-0.04, 0.04	0.91	
					placebo	74	g/cm ²	0.697	final=0.7 88	sd=0.121				
		whole body BMD			10 µg Vit D ₃ /day	74	g/cm ²	0.872	final=0.9 17	sd=0.080	+0.01	-0.02, 0.03	0.53	
					5 µg Vit D ₃ /day	73	g/cm ²	0.866	final=0.9 15	sd=0.075	+0.01	-0.02, 0.03	0.63	
					placebo	74	g/cm ²	0.863	final=0.9 09	sd=0.075				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Macdonald 2013 ²⁴⁵		whole body BMC			10 µg Vit D ₃ /day	74	g	1308	final=156 1	sd=366	+38	-74, 150	0.50	A
					5 µg Vit D ₃ /day	73	g	1311	final=155 9	sd=324	+36	-70, 142	0.50	
					placebo	74	g	1277	final=152 3	sd=324				
	total hip BMD		1°	1 yr	Vit d3 400 IU	83	g/cm 2	0.917	final= 0.912	sd=0.103	-0.002	-0.036, 0.032	0.91	
					Vit d3 1000 IU	88		0.923	final= 0.923	sd=0.135	+0.009	-0.029, 0.047	0.64	
					placebo	88		0.92	final= 0.914	sd=0.118				
					Vit d3 400 IU	83		1.075	final= 1.076	sd=0.135	+0.006	-0.038, 0.050	0.79	
					Vit d3 1000 IU	88		1.068	final= 1.071	sd=0.164	+0.001	-0.046, 0.048	0.97	
	total lumbar spine BMD				placebo	88		1.081	final= 1.070	sd=0.153				

^ABaseline/final sample size

^B Downgraded to C because very small sample size (insufficient power) and no adjustments for confounders

^CEstimated from available data

Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor Assay						
Zhu 2008 ²⁶⁶ Beijing, China	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 10.1 (SD 0.3) 0%	Vit D intake Control group – 0.9 ± 0.6µg/d CaD milk – 0.9 ± 0.6µg/d	560 mg calcium + 5-8 µg Vit D/school day Vs. control (no supplementary milk and habitual diet)	nd	
Zhu 2008 ²⁷⁵ CIFOS Western Australia [18089701]	<ul style="list-style-type: none"> • 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)	
Radioimmunoassay						
Bolton-Smith 2007 ²⁷⁴ (UK 54°N) [17243866]	<ul style="list-style-type: none"> • 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.
Islam 2010 ²⁶⁷ Dhaka, Bangladesh	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 22.9 (SD 3.9) 0%	placebo-35.0 +/-9.4 nmol/L Vit D-37.1 +/-12.1 nmol/L VitD+Ca- 37.8 +/-10.9 nmol/L MMN+D+Ca- 36.9 +/-12.5 nmol/L	VD (Vit D 10 µg)/day Vs. VD-Ca (Vit D 10 µg + calcium 600 mg)/day Vs. Placebo	compliance not given but 18.5% dropped out	
Jackson 2011 ²⁶⁸ WHI US (various)	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Post menopausal nd 0%	vitamin D intake: placebo- 7.54 +/-6.36 ug/d, CaD- 7.42 +/-5.84 ug/d calcium intake: placebo- 1049 +/-625.7 mg/d, CaD- 1,039 +/-635.1 mg/d	(400 IU Vit D ₃ +1000 mg elemental calcium)/day Vs. placebo	80% or greater compliance-968 women (placebo = 500, CaD= 468)	
Karkkainen 2010 ²⁶⁹ OSTPRE-FPS Kuopio, Finland	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Post menopausal 67.4 (SD 1.9) 0%	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)	Vit D 800 IU+calcium 1,000 mg Vs. control (neither supplementation nor placebo)	79% compliance	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Kukuljan 2011 ²⁷² Geelong, Australia	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 59.9 (SD 7.4) 100%	calcium intake: 911–1064 mg/d Serum vitamin D level: 86.3+/-36.0 nmol/L	fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃) vs. controls	exercise program- 63% (95% CI: 57, 69) fortified milk- 90% (95% CI, 87, 93),	
Cheng 2005 ²⁷³ Jyväskylä, Finland (62°24'N) [16280447]	<ul style="list-style-type: none"> • 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	
Assay method not reported						
Moschonis 2006 ²⁷⁶ Greece (31°N) [17181890]	<ul style="list-style-type: none"> • 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
Moschonis 2010 ²⁷⁰ Postmenopausal Health Study Greece	<ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) 	Healthy 60.7 (SD 5) 0%	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level: 26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months Vs. control (neither counselling nor dietary products)	nd	
Moschonis 2011 ²⁷¹ Postmenopausal Health Study Greece	<ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) 	Healthy 62.4 (SD 5.3) 0%	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d	CaD (800 mg calcium+10 µg Vit D ₃)/day Vs. control	NR	

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followu p, mo	Interventions , Daily Dose	No. Analyz ed	Unit	Baselin e	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Qualit y	
Radioreceptor Assay															
Zhu 2008 ²⁶⁶	9-18 yrs	midriff BMDsc	1°	2 yr	560 mg calcium + 5-8 µg Vit D/school day	112	mg/cm ₈₆ ^{1.5}	1585	final=1803	sd=446	+43	-79, 165	0.49	B	
					control (no supplementary milk and habitual diet)	123	mg/cm ₈₆ ^{1.5}	1584	final=1760	sd=499					
					560 mg calcium + 5-8 µg Vit D/school day	112	mg/cm ₈₂ ^{3.0}	46	final=49	sd=7	0	-1.9, 1.9	1		
					control (no supplementary milk and habitual diet)	123	mg/cm ₈₂ ^{3.0}	47	final=49	sd=8					
		pelvis BMDsc			560 mg calcium + 5-8 µg Vit D/school day	112	mg/cm ₈₂ ^{3.0}	46	final=49	sd=7	0	-1.9, 1.9	1		
					control (no supplementary milk and habitual diet)	123	mg/cm ₈₂ ^{3.0}	47	final=49	sd=8					
					total body BMDsc	560 mg calcium + 5-8 µg Vit D/school day	112	mg/cm ₂₈ ^{2.5}	93	final=95	sd=10	+3	0.3, 5.7		0.03
						control (no supplementary milk and habitual diet)	123	mg/cm ₂₈ ^{2.5}	95	final=92	sd=11				
Hip BMD	Postmenopausal women	1°	60	Vit D ₂ 1000 IU + Ca citrate 1200 mg		39/33 ^B	mg/cm ²	783	nd		2.20%	1.9, 2.5	0.05	B	
				Placebo		41/36 ^B		828	nd						
Radioimmunoassay															
Bolton-Smith 2007 ²⁷⁴ [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					
Islam 2010 ²⁶⁷		Femoral neck BMC			VD (Vit D 10 µg)/day	40	g	3.384	change=0.061	sd=0.205	+0.14	0.05, 0.22	<0.001		

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followu p, mo	Interventions , Daily Dose	No. Analyz ed	Unit	Baselin e	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Qualit y		
	9-18, 19-50 yrs	Femoral neck BMD	1°	1 yr	VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	3.436	change=0.0 69	sd=0.174	+0.14	0.07, 0.22	<0.001	A		
					Placebo	35	g	3.316	change=- 0.075	sd=0.146						
					VD (Vit D 10 µg)/day	40	g/cm ²	0.8	change=0.0 12	sd=0.028	+0.02	0.01, 0.03	<0.001			
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm ²	0.799	change=0.0 13	sd=0.030	+0.02	0.01, 0.03	<0.001			
		Lumbar spine L2-L4 BMC			Placebo	35	g/cm ²	0.768	change=- 0.010	sd=0.012						
					VD (Vit D 10 µg)/day	40	g	32.548	change=0.6 20	sd=2.442	+0.58	-0.84, 2.00	0.42			
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	31.782	change=0.6 87	sd=2.761	+0.65	-0.82, 2.12	0.39			
					Placebo	35	g	32.399	change=0.0 42	sd=3.673						
		Lumbar spine L2-L4 BMD			VD (Vit D 10 µg)/day	40	g/cm ²	0.898	change=0.0 13	sd=0.036	+0.02	-0, 0.04	0.12			
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm ²	0.895	change=0.0 10	sd=0.042	+0.01	-0.01, 0.03	0.22			
					Placebo	35	g/cm ²	0.891	change=- 0.003	sd=0.049						
		Trochanter BMC			VD (Vit D 10 µg)/day	40	g	5.818	change=0.1 58	sd=0.549	+0.31	0.09, 0.53	0.01			
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	5.877	change=0.0 90	sd=0.419	+0.24	0.06, 0.43	0.01			
					Placebo	35	g	5.885	change=- 0.151	sd=0.389						
		Trochanter BMD			VD (Vit D 10 µg)/day	40	g/cm ²	0.634	change=0.0 02	sd=0.021	+0.02	0.01, 0.03	0.002			

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
		Ward's triangle BMD			VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm ²	0.625	change=0.001	sd=0.026	+0.02	0.01, 0.03	0.01	
					Placebo	35	g/cm ²	0.619	change=-0.017	sd=0.029				
					VD (Vit D 10 µg)/day	40	g/cm ²	0.654	change=0.010	sd=0.035	+0.03	0.01, 0.04	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm ²	0.654	change=0.015	sd=0.031	+0.03	0.02, 0.05	<0.001	
					Placebo	35	g/cm ²	0.628	change=-0.018	sd=0.027				
					Jackson 2011 ²⁶⁸	Postmenopausal	Intertrochanteric BMD	1°	year 6	(400 IU Vit D ₃ +1000 mg elemental calcium)/day	777	g/cm ²	0.746	
placebo	751		0.725	final=0.725						sd=0.137				
Narrow neck BMD	(400 IU Vit D ₃ +1000 mg elemental calcium)/day	777		0.736			final=0.742			sd=0.133	+0.02	0.01, 0.03	0.003	
	placebo	751		0.723			final=0.722			sd=0.136				
Shaft BMD	(400 IU Vit D ₃ +1000 mg elemental calcium)/day	777		1.18			final=1.199			sd=0.189	+0.03	0.01, 0.05	<0.001	
	placebo	751		1.155			final=1.165			sd=0.190				
Karkkainen 2010 ²⁶⁹	51-70 yrs	Femoral neck BMD	1°	3 yr	Vit D 800 IU+calcium 1,000 mg	280	g/cm ²	0.866	final=0.848	sd=0.13	-0.002	-0.02, 0.02	0.85	C
					control (neither supplementation nor placebo)	311		0.865	final=0.850	sd=0.12				
		Lumbar spine BMD			Vit D 800 IU+calcium 1,000 mg	259		1.039	final=1.047	sd=0.17	0.013	-0.04, 0.02	0.37	

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followu p, mo	Interventions , Daily Dose	No. Analyze d	Unit	Baselin e	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Qualit y
		Total body BMD	1°	18 months	control (neither supplementati on nor placebo)	285		1.052	final=1.060	sd=0.17				
					Vit D 800 IU+calcium 1,000 mg	195		1.069	final=1.078	sd=0.10	-0.003	-0.02, 0.02	0.76	
		Total proximal femur BMD			control (neither supplementati on nor placebo)	238		1.079	final=1.081	sd=0.10				
					Vit D 800 IU+calcium 1,000 mg	280		0.948	final=0.934	sd=0.14	-0.005	-0.03, 0.02	0.65	
		Trochanter BMD			control (neither supplementati on nor placebo)	310		0.953	final=0.939	sd=0.13				
					Vit D 800 IU+calcium 1,000 mg	280		0.783	final=0.779	sd=0.13	-0.01	-0.03, 0.01	0.31	
		Ward's triangle			control (neither supplementati on nor placebo)	310		0.797	final=0.790	sd=0.13				
					Vit D 800 IU+calcium 1,000 mg	280		0.67	final=0.652	sd=0.14	-0.001	-0.02, 0.02	0.93	
		L1-L3 total volumetric BMD			control (neither supplementati on nor placebo)	310		0.672	final=0.653	sd=0.13				
					fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃)	45	g/cm ³	164	change=-0.6	-2.1, 0.8	-0.6	-2.7, 1.6	0.61	
		Kukuljan 2011 ²⁷²			51-70, 71+ yrs				controls	44		171	change=-	-1.5, 1.4

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				
		L1-L3 trabecular volumetric BMD			0.05													
					fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃)	45	115	change=-1.5	-3.1, 0.9	-2.3	-6.4, 1.8	0.26						
					controls	44	120	change=0.8	-2.9, 1.2									
					fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃)	45	1104	change=-1.0	-1.4, -0.6	-0.3	-1.0, 0.4	0.41						
		mid-femur cortical volumetric BMD			controls	44	1108	change=-0.7	-1.3, -0.2									
		mid-tibia cortical volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D ₃)	45	1105	change=-1.2	-1.7, -0.7	-0.1	-0.8, 0.6	0.78						
					controls	44	1113	change=-1.1	-1.6, -0.5									
					Enzyme-linked Immunoabsorption Assay													
					Cheng 2005 ²⁷³ [16280447]	10-12 y girls	BMC	1°	24	Vit D 200 IU + Ca carbonate 1000 mg	46	kg	1.3	34.70%	34.3%, 35.1%	-0.3%	-0.8, 0.2 ^A	NS
									Placebo	39		1.3	35.00%	34.6%, 35.4%				
Assay method not reported																		
Moschonis 2006 ²⁷⁶ [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	1.50%	0.9%, 2.2%	2.20%	1.3, 3.1 ^A	<0.05	C				
					Control (usual diet)	36		1.12	-0.70%	-1.4%, -0.1%								
Moschonis 2011 ²⁷¹		heel BMD	1°	12 months	CaD (800 mg calcium+10 µg Vit D ₃)/day	26	g/cm ²	0.476	final=0.459	sd=0.081	-0.002	-0.04, 0.04	0.92					

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
Postmenopausal Health Study	Postmenopausal	L2-L4 BMD	1°	30 months	control	39		0.472	final=0.461	sd=0.083				B
					CaD (800 mg calcium+10 µg Vit D ₃)/day	26		1.121	final=1.113	sd=0.160	+0.01	-0.07, 0.10	0.77	
					control	39		1.134	final=1.101	sd=0.167				
		total body BMD			CaD (800 mg calcium+10 µg Vit D ₃)/day	26		1.112	final=1.135	sd=0.083	+0.04	0, 0.08	0.05	
					control	39		1.095	final=1.094	sd=0.079				
					Moschonis 2010 ²⁷⁰ Postmenopausal Health Study	pelvis BMD	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months	35	g/cm ²	1.096	final=1.089	sd=0.087	+0.02	
control (neither counselling nor dietary products)	31		1.067	final=1.067			sd=0.084							
total body BMD	(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months	35		1.134			final=1.135	sd=0.067	+0.03	-0.01, 0.06	0.11			
	control (neither counselling nor dietary products)	31		1.124		final=1.106	sd=0.078							

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followu p, mo	Interventions , Daily Dose	No. Analyze d	Unit	Baselin e	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Qualit y
		total spine BMD			(1200 mg calcium+7.5 µg D ₃)/day for the first 12 months + (1200 mg calcium+22.5 µg D ₃)/day for the next 18 months control (neither counselling nor dietary products)	35		1.119	final=1.234	sd=0.135	+0.04	-0.03, 0.11	0.23	
						31		1.139	final=1.193	sd=0.139				

^A Estimated from reported data.

^B Baseline/followup number of subjects analyzed.