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Vitamin D and Calcium: A Systematic Review of Health Outcomes

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Prepared by:

Tufts Evidence-based Practice Center, Boston, MA

Investigators:

Mei Chung, M.P.H.
Ethan M Balk, M.D., M.P.H.
Michael Brendel, B.A.
Stanley Ip, M.D.
Joseph Lau, M.D.
Jounghee Lee, Ph.D.
Alice Lichtenstein, D.Sc.
Kamal Patel, M.B.A., M.P.H.
Gowri Raman, M.D.
Athina Tatsioni, M.D., Ph.D.
Teruhiko Terasawa, M.D.
Thomas A Trikalinos, M.D., Ph.D.

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Preface

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

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

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

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

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Beth A. Collins Sharp, R.N., Ph.D.
Director, EPC Program
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

Paul M. Coates, Ph.D.
Director, Office of Dietary Supplements
National Institutes of Health

Elizabeth A. Yetley, Ph.D.
Senior Nutrition Research Scientist, Retired
Office of Dietary Supplements
National Institutes of Health

Mary Frances Picciano, Ph.D.
Senior Nutrition Research Scientist
Office of Dietary Supplements
National Institutes of Health

Kimberly D. Elmslie, M.Sc.
Director General
Centre for Chronic Disease Prevention and
Control
Public Health Agency of Canada

Margaret de Groh, Ph.D.
Manager, Risk Factors Unit
Centre for Chronic Disease Prevention and Control
Health Canada

Hasan Hutchinson, Ph.D., N.D.
Director General
Office of Nutrition Policy and Promotion
Public Health Agency of Canada

Linda Greene-Finestone, Ph.D., R.D.
Nutrition Advisor
Centre for Chronic Disease Prevention and Control
Public Health Agency of Canada

Paula R. Trumbo, Ph.D.
Supervisor, Nutrition Science Evaluation
Office of Nutrition, Labeling and Dietary
Supplements
Center for Food Safety and Applied
Nutrition
Food and Drug Administration

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Steven Abrams, M.D.
Professor of Pediatrics
Baylor College of Medicine
Section of Neonatology
Texas Children's Hospital
Houston, Texas

Glennville Jones, Ph.D.
Professor and Head
Department of Biochemistry
Queen's University
Ontario, Canada

Stephanie Atkinson, Ph.D.
Professor and Associate Chair
Department of Pediatrics
Biochemistry and Biomedical Sciences
Health Sciences
McMaster University
Hamilton, Canada

Susan Taylor Mayne, Ph.D., F.A.C.E.
Professor
Division of Chronic Disease Epidemiology
Yale School of Public Health
New Haven, Connecticut

Patsy M. Brannon, Ph.D.
Professor
Division of Nutritional Sciences
Cornell University
Ithaca, New York

Clifford J. Rosen, M.D.
Senior Scientist
Maine Medical Center Research Institute
Scarborough, Maine

Rebecca D. Jackson, M.D.
Associate Professor
Department of Internal Medicine
Division of Endocrinology, Diabetes, and
Metabolism
The Ohio State University
Columbus, Ohio

Structured Abstract

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

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

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

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

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

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

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

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

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

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Appendixes and Evidence Tables for this report are provided electronically at <http://www.ahrq.gov/downloads/pub/evidence/pdf/vitadcal/vitadcal.pdf>.

Evidence Report

Chapter 1. Introduction

Background

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

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

Sources, Metabolism and Functions of Vitamin D

Vitamin D was classified as a vitamin in the early 20th century and in the second half of the 20th century as a prohormone (“conditional” vitamin).^{7,8} There are two forms of vitamin D, vitamin 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.

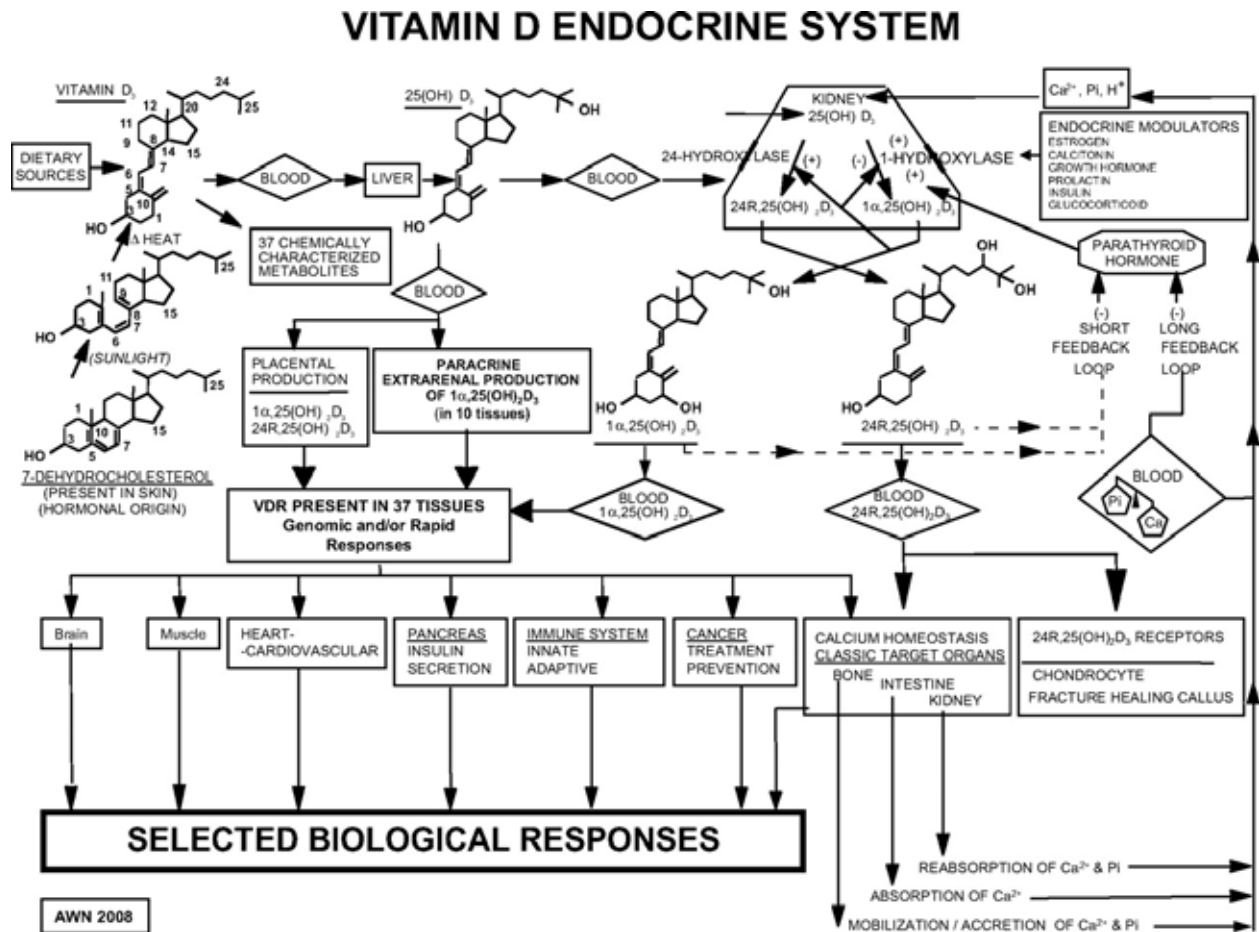
In its native form vitamin D is not biologically active, the active form is 1,25(OH)₂D. The conversion of vitamin D to 1,25(OH)₂D requires two hydroxylation in tandem. Vitamin D is first hydroxylated by the liver to form 25(OH)D, which is then hydroxylated by the kidney to form 1,25(OH)₂D. 25(OH)D has low biological activity, but it is the major form of vitamin D that circulates in the blood stream. Serum 25(OH)D concentrations are generally thought to reflect nutritional status.^{7,8} When adequate amounts of vitamin D are available, the kidney, the major site of 1,25(OH)₂D production converts some of the 25(OH)D to alternate hydroxylated metabolites, which have low biological activity (e.g., 24,25(OH)₂D or 1,24,25(OH)₃D). Renal synthesis of 1,25(OH)₂D is tightly regulated by plasma parathyroid hormone, together with serum calcium and phosphorus concentrations. Additional tissues that express the enzyme that catalyses the conversion of 25(OH)D to 1,25(OH)₂D, 25-hydroxyvitamin D3-1- α -hydroxylase, include colon, prostate, mammary gland, macrophages, antigen-presenting cells, osteoblasts and keratinocytes.⁹

Vitamin D has both genomic and nongenomic functions. For the genomic functions, 1,25(OH)₂D interacts with nuclear vitamin D receptors to influence gene transcription. Nuclear receptors for 1,25(OH)₂D have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle and skin. For the nongenomic functions, 1,25(OH)₂D acts like a steroid hormone, working through activation of signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include intestine, bone, parathyroid, liver and pancreatic beta cells. Biological actions include increases in intestinal calcium absorption, transcellular calcium flux and opening gated calcium channels allowing calcium uptake into cells such as osteoblasts and skeletal muscle.

One of the major biological functions of vitamin D is to maintain calcium homeostasis which impacts on cellular metabolic processes and neuromuscular functions. Vitamin D affects intestinal calcium absorption by increasing the expression of the epithelial calcium channel protein, which in turn enhances the transport of calcium through the cytosol and across the basolateral membrane of the enterocyte. Vitamin D also facilitates the absorption of intestinal phosphate. 1,25(OH)₂D indirectly affects bone mineralization by maintaining plasma calcium and phosphorus concentrations, and subsequently extracellular calcium and phosphorus concentrations at the supersaturating range necessary for mineralization. 1,25(OH)₂D, in concert with parathyroid hormone, also causes demineralization of bone when calcium concentrations fall to maintain plasma concentrations within a narrow range. It has yet to be determined whether 1,25(OH)₂D directly influences bone mineralization.

In addition to intestine and bone, a wide range of other tissues and cells that are influenced by vitamin D. Five biological systems have vitamin D receptors and are responsive to $1,25(\text{OH})_2\text{D}$, as summarized in Figure 1.¹⁰ These systems include immune, pancreas, cardiovascular, muscle and brain; and control of cell cycle. The biological effects of $1,25(\text{OH})_2\text{D}$ are diverse. For example, as recently noted, $1,25(\text{OH})_2\text{D}$ inhibits PTH secretion and promotes insulin secretion, inhibits adaptive immunity and promotes innate immunity, and inhibits cell proliferation and stimulates their differentiation.¹¹ A number of recent reviews have appeared on these topics.¹⁰⁻¹⁷

Figure 1. Summary of the vitamin D endocrine system



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

Sources, Metabolism, and Functions of Calcium

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

absorption is dependent on $1,25(\text{OH})_2\text{D}$. 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 percent), primarily albumin and prealbumin, complexed with sulfate, phosphate or citrate (~10 percent), and in the ionized form (~50 percent). Blood calcium concentrations are controlled extracellularly by parathyroid hormone, calcitriol and calcitonin. Intracellular calcium concentrations are maintained at relatively low levels. Increased intracellular calcium concentrations occur in response to second messengers by stimulating release from intracellular sites (endoplasmic reticulum, mitochondria) and hormones by facilitating influx from extracellular sites by transmembrane diffusion or channels.

Calcium balance measures provide information on calcium absorption relative to calcium loss in urine, sweat and endogenous intestinal secretions. During periods of growth, positive calcium balance implies bone mineralization but does not provide an indication of whether the rate of bone mineralization is optimal. During adulthood negative calcium balance implies calcium lost from bone but does not provide an indication of which site(s). Calcium 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. These functions of calcium are frequently classified into the following general categories; bone development and maintenance, blood clotting, transmission of nerve impulses to target cells, muscle contraction and cell metabolism. In addition, calcium may play a role in colon cancer, kidney stones, blood pressure, body weight and lead absorption.

Challenges for the DRI Committees

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

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

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

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

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

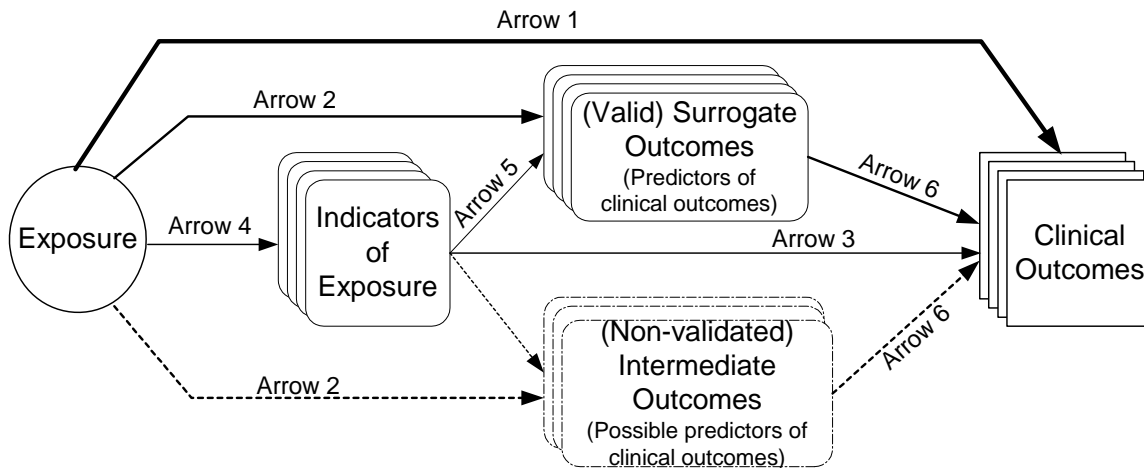
Key Questions Addressed in this Report

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

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

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

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



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

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

Chapter 2. Methods

Overview

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

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

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

Sponsoring Federal agencies.

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

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

AHRQ Task Order Officer (TOO).

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

Technical Expert Panel (TEP).

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

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

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

EPC methodologists.

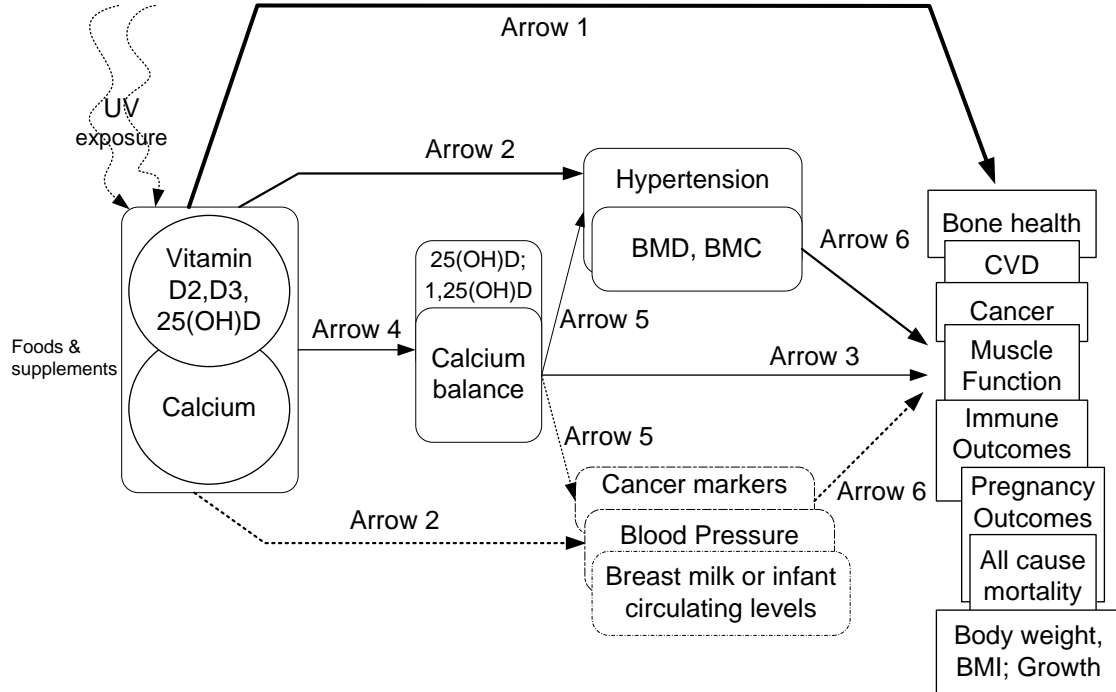
This evidence report was carried out under the AHRQ EPC program, which has a 12-year history of producing over 175 evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continually refine approaches to conducting evidence reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. The Tufts EPC has produced many evidence reports on nutrition topics¹⁹⁻²⁴ (<http://www.ahrq.gov/clinic/epcix.htm>). We have also conducted methodological research to identify the issues and challenges of including evidence-based methods as a component of the process used to develop nutrient reference values, such as the DRI, using vitamin A as an example.³

Development of the Analytic Framework and Refinement of Key Questions

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

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

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



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

Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have good or possible evidence for linkage with clinical outcomes, respectively). (Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with dashed outline.)

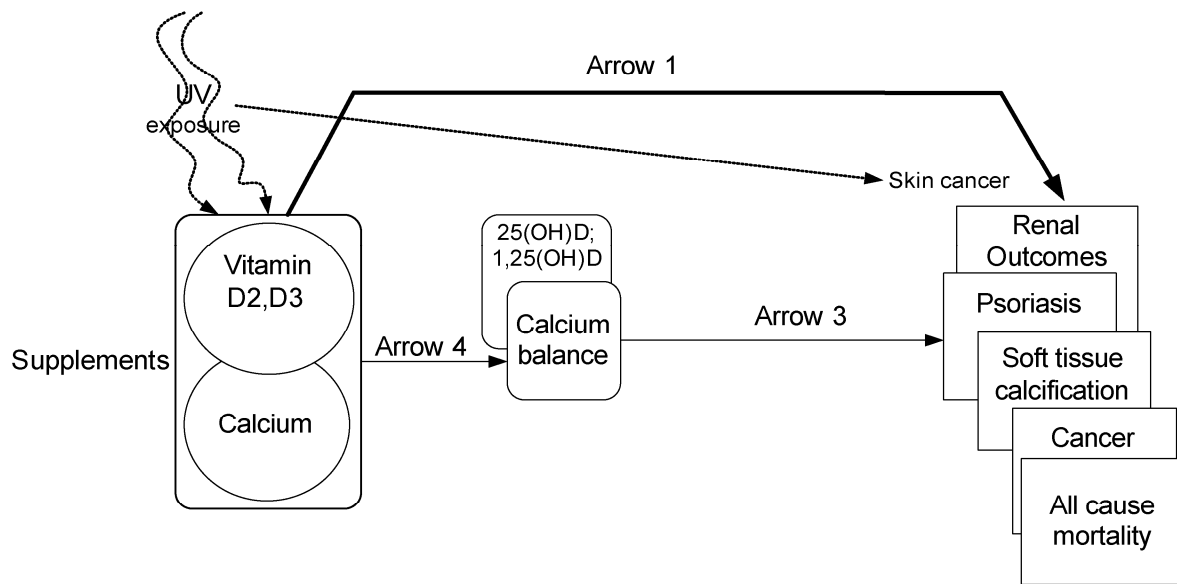
Arrow 3: Association of indicators of exposure to clinical outcomes.

Arrow 4: Association between exposure and indicators of exposure.

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

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

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



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

Definitions

Vitamin D and Calcium Exposures

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

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

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

Clinical Outcomes

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

Indicators of Exposure (Nutrient Intake)

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

Indicators of vitamin D exposure (i.e., vitamin D intake and sun exposure) included serum 25(OH)D and 1,25(OH)₂D concentrations.

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

Surrogate Outcomes

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

Intermediate Outcomes

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

Life Stages

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

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

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

Key Questions

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

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

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

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

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

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

Literature Search Strategy

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

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

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

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

Study Selection

Abstract Screening

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

Full Text Article Eligibility Criteria

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

Primary studies.

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

General eligibility criteria for the full text articles were:

Population of interest:

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

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

Intervention/exposure of interest.

- For observational studies:
 - Serum 25(OH)D or 1,25(OH)₂D concentration
 - Dietary intake level of vitamin D were not included due to inadequacy of nutrient composition tables for vitamin D.²⁵
 - Dietary intake level of calcium from food and/or supplements
 - Calcium balance (i.e., calcium accretion, retention, and loss)
- For interventional studies:
 - Vitamin D supplements (but not analogues) with known doses
 - Calcium supplements with known doses
 - The only combination of dietary supplements of interest was the combination of vitamin D and calcium. Any other combinations of supplements and/or drug treatments were excluded unless the independent effects of vitamin D and/or calcium can be separated. Thus studies of multivitamins were excluded.
 - Trials in which participants in both study groups took the same calcium (or vitamin D) supplement were evaluated as vitamin D (or calcium) versus control trials. In other words, the intervention common to both study groups was ignored (though it was noted).
 - Food based interventions were included if the doses of vitamin D and/or calcium were quantified and there were differences in the doses between the comparison groups. For example, a trial of dairy supplementation (with 500 mg/d calcium) versus no supplementation was qualified to be included. However, a trial of calcium fortified orange juice (with 1200 mg/d calcium) versus milk (with 1200 mg/d calcium) was not qualified to be included because there are no differences in the calcium doses.
 - Non-oral routes of nutrient delivery were excluded

Specific outcomes of interest.

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

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

Study design.

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

Systematic reviews.

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

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

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

Other Specific Eligibility Criteria

- Growth outcomes (weight and height gain)
 - Only infants (<1 year old) and children (age <18 years old) were included
 - For infants, we include all eligible study designs. The vitamin D and/or calcium intervention or exposure can be administered to the mothers or to the infants in the study.
 - For infants, premenarchal girls, and boys of similar age, only RCTs that reported weight as a primary or secondary outcome were included. RCTs of weight loss were excluded.
- Cardiovascular disease clinical outcomes
 - Only adults (aged ≥ 18 years old) were included.
- Blood pressure and body weight
 - Only adults (aged ≥ 18 years old) were included.
 - Only RCTs of calcium or vitamin D interventions were included. We did not include observational studies of associations between calcium or vitamin D intake or serum vitamin D concentrations and blood pressure or weight measurements (as continuous outcomes). This decision was made in agreement with the TEP in part because it was agreed that any conclusions based on observational studies (e.g., associations between baseline calcium intake and change in systolic blood pressure) would be weak and difficult to interpret.
- Bone health clinical outcomes
 - The Ottawa EPC report⁶ 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 report⁶ was updated with literature published between January 2006 and September 2008. For adults, we included only BMD indices. For children, we included only BMC indices. Only RCTs with duration of more than 1 year were qualified for inclusion.
 - Studies of calcium and bone health clinical outcomes were excluded.
- Dose-response relationship between intake levels and indicators of exposure (arrow 4 of Figures 2 and 3)
 - Studies for this question were identified in our literature search that crossed vitamin D terms with various outcomes terms. Some studies that addressed this question but do not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all full text articles mentioning vitamin D supplements (in excess of 10,000) to look for data on serum 25(OH)D concentration.

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

Data Extraction

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

Data extraction forms (evidence tables) were developed separately for extraction of systematic reviews and primary studies. For primary studies, the items extracted were: study characteristics, baseline population characteristics, background diet data, dietary assessment methods for calcium intake, 25(OH)D assay methods, interventions (for interventional studies only), confounders and effect modifiers that were adjusted for in statistical analysis, results, and quality assessments. Whenever the type of vitamin D supplement (D₂ or D₃) was clearly reported, we extracted and reported this information. Otherwise, we used the general term “vitamin D”. Evidence tables for all eligible studies are available in Appendix C. For systematic reviews, items extracted were: design, population, intervention (exposure) and comparator, results, and AMSTAR²⁶ checklist criteria (a measurement tool created to assess the methodological quality of systematic reviews). A table with a list of all systematic reviews with the evaluation of their relevance to this report, and evidence tables of the qualified systematic reviews are available in Appendix D.

Data Analysis

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

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

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

where SE₁, SE₂, and SE₁₂ are the SEs for baseline, final and change, respectively, and ρ is the correlation between the baseline and final measurements.²⁷ We arbitrarily chose the correlation, ρ, to be 0.50, the midpoint value. In our experience, using different values for ρ generally does not greatly affect the meta-analysis results of quantitative analyses or conclusions.

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

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

Meta-analysis

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

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

Grading of Studies Analyzed in This Evidence Report

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

Critical Appraisal and Grading of Primary Studies

Critical appraisal of the evidence is an important aspect of conducting a systematic review. For the assessment of interventional studies, the criteria were based on the CONSORT³¹ statement for reporting RCTs (a checklist with specifications for reporting important aspects of a trial). We primarily considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of well-described valid primary outcomes, and the dropout rate.

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

For the assessment of prospective cohorts and nested case-control studies (cross-sectional and retrospective case-control studies were excluded from this review), we developed a rating checklist specifically designed for nutritional epidemiology study based on some of the reporting items for cohort study in STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist³² and the nutrition-specific items in our previous publication.³³ Items assessed include: eligibility criteria and sampling of study population, blinding of exposure and outcome assessors, dietary assessment methodology (when applicable), assay methodology of biomarkers of intake (when applicable), clear reporting of comparisons in the study, statistical analyses, adequacy of controlling for baseline characteristics and prognostic factors (including confounders), clear reporting of outcome definitions, and prospective study design with preplanned hypotheses.

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

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

A

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

B

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

C

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

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

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

Randomized controlled trials of all outcomes.

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

Observational studies of cancer outcomes.

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

Critical Appraisal of Systematic Reviews

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

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

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

Reporting of the Evidence

Evidence tables.

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

Summary tables.

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

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

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

Graphical presentation of dose-response relationship.

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

Grand summary tables (evidence map).

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

Units of measurement.

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

Assay method.

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

Sunlight exposure.

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

Primary and secondary outcomes.

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

Study quality.

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

Organization of the results section.

The Results section is organized in the following way:

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

Chapter 3. Results

Literature Search Results

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

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

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

Figure 5. Literature flow in this report

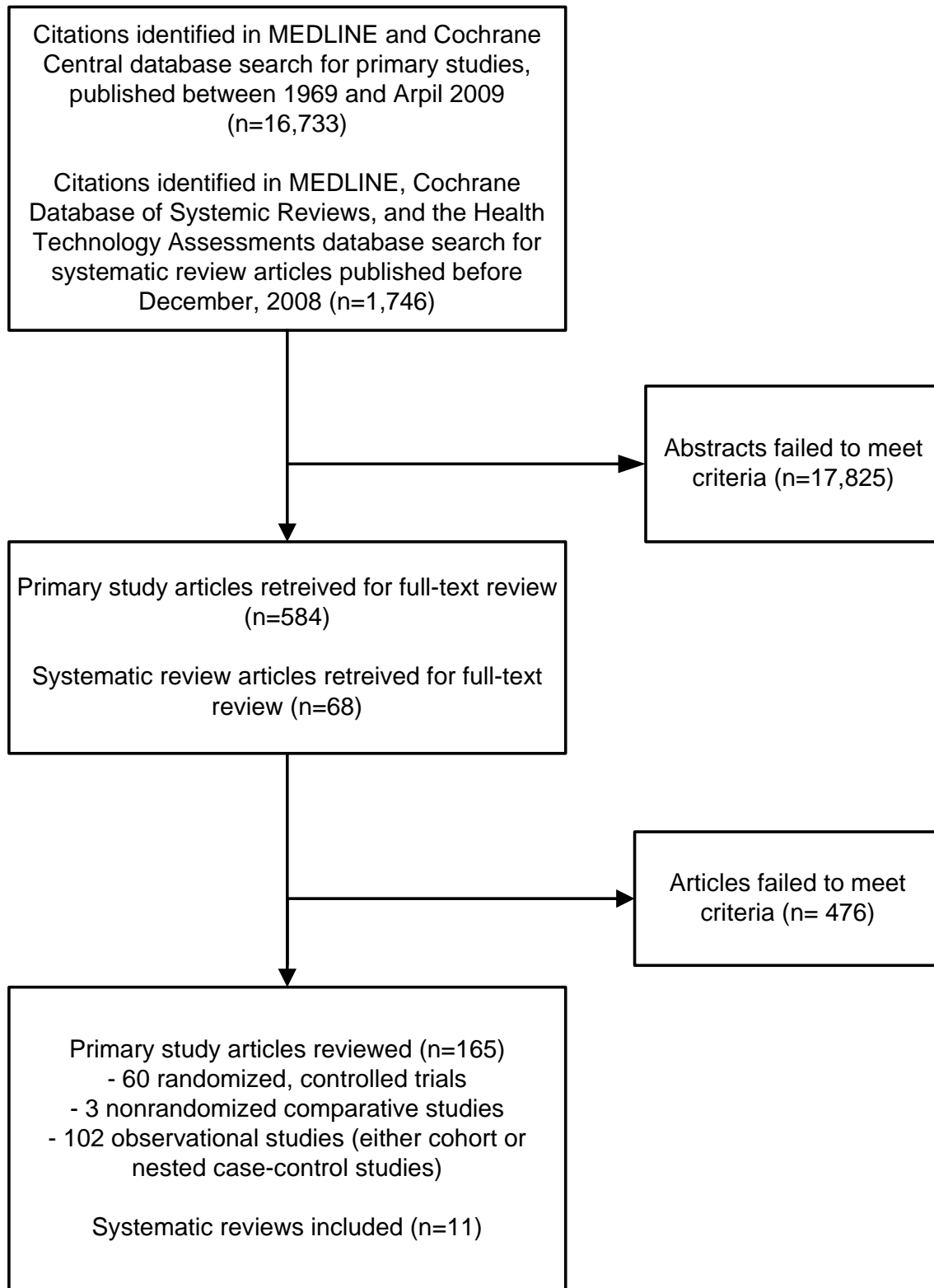


Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages

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

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

^A Only RCTs were eligible for this outcome

^B Relationship between maternal 25(OH)D concentration and atopic eczema in infants

^C 1 study was a combined analysis of Nurses Health Study and Health Professionals Follow-up Study

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

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

^A Only RCTs were eligible for this outcome

^B Association between total calcium intake in childhood and colorectal cancer after 65 years of followup

^C 1 study was a combined analysis of Nurses Health Study and Health Professionals Follow-up Study

^D 6 analyses, including 2 separate analyses of NHANES I

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

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

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

^A Only RCTs were eligible for this outcome

^B Including the Women's Health Initiative (WHI) trial

^C A de novo reanalysis of the 10 RCTs in a previous systematic review and one newly added trial

Vitamin D and Health Outcomes

Vitamin D and Growth

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

Synopsis.

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

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

Six RCTs³⁴⁻⁴⁰ and one nonrandomized comparative study⁴¹ in eight publications reported on the effect of vitamin D supplementation on growth parameters in infants and children. Two cohort studies reported on the association between maternal serum 25(OH)D concentration and her offspring's growth parameters.^{42,43} The number of subjects in the RCTs ranged from 19 to 200. The two cohort studies had 374 and 466 subjects, respectively. The latitudes of the studies ranged from 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. Followup ranged from delivery until 9 years. Methodological quality of two studies were rated B and seven studies were rated C. The studies were limited by such factors as incomplete reporting and small sample sizes.

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

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

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

9 - 18 years.

One RCT of vitamin 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 followup in weight or height among the 34 girls who were premenarchal at time of enrollment.³⁵

Findings by life stage.

- **0 – 6 mo** One RCT found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length. Another RCT found that supplementing expectant mothers with a total of 1.2 million IU of vitamin D during the 3rd trimester effected a significant increase in birth weight (+190 g). Background diet is low in vitamin D in this study. A study compared supplementing lactating mothers with vitamin D 400 IU/d and their infants 300 IU/d for 6 months with mothers supplemented with 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age. Another study compared supplementing newborn infants with 100, 200, or 400 IU/d of vitamin D for 6 months and reported no significant difference in weight or length at 6 months of age. An RCT supplemented expectant mothers with either vitamin D 1000 IU/d during the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods. A cohort study analyzed the maternal serum 25(OH)D concentration at 28-32 week gestation (geometric mean in winter 48 nmol/L; summer 69 nmol/L) and found no association with infant birth weight or length. Another cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.
- **7 mo – 2 y** A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.
- **3 – 8 y** No study covered this life stage.
- **9 – 18 y** A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years. One RCT of vitamin D₃ (placebo, 200, or 2000 IU/d for 1 year) on girls 10-17 years old found no significant difference at 1 year followup in weight or height among the girls who were premenarchal at time of enrollment.
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|---|--|---|--|--|
| RCTs | | | | | |
| Maxwell 1981 ³⁸ Brooke 1980 ³⁴ UK (51°N) [6793058] [6989438] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | pregnancy nd 0 | 25(OH)D at 28-32 wk: 20.1 nmol/L | Vit D 1000 IU/d 3 rd trimester only | nd First generation Asian immigrants only |
| Feliciano 1994 ³⁶ 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 |
| El-Hajj 2006 ³⁵ Lebanon (33°N) [16278262] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | healthy 13.2 (10-17) 0 | 25(OH)D 35 nmol/L; dietary Ca 677 mg/d | Vit D ₃ 200 IU/d vs. 2000 IU/d vs. placebo x 1 y | 98% in placebo; 98% in low dose; 97% in high dose 7.4 h sun exposure/wk |
| Wagner 2006 ³⁹ Charleston, US (32°N) [17661565] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Fully lactating; <1 mo postpartum 29 0 | Lactating mother's dietary Vit D 273 IU/d; dietary calcium intake: 1125 mg/d; | Mother Vit D ₃ 400 IU/d + infant 300 IU/d vs. mother 6400 IU/d + infant 0 IU/d | ≥80% in mothers; as low as 61% for infants 78% white; 11% black; 11% Hispanic |
| Marya 1988 ³⁷ India (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 |
| Mallet 1986 ⁴⁰ France (48°N) [3755517] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | pregnancy newborn nd | Ca intake 550 to 1000 mg/d in 55% of the subjects | Vit D 1000 IU/d vs. 200,000 IU 1x dose | nd |
| Nonrandomized comparative study | | | | | |
| Marya 1981 ⁴¹ India (28°N) [7239350] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | no pregnancy-related complications nd 0 | Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d | Vit D 1200 IU/d + Ca 375 mg/d (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 5. Vitamin D and growth outcomes: Characteristics of cohort studies

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|---|---|--|--|--|---|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Morley 2006 ⁴³ Australia (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 ⁴² 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 6. Vitamin D and growth outcomes: Results of RCTs

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

Continued

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change (SD) | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|--|--------------------------------------|-----------------|-------|------------------|------------------------------|-----------------|------|----------|-----------------------|------------------|--------------|--------------------|-------|------------------|
| Mallet 1986 ⁴⁰ France (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) | | | | | |

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

^B See Table 3 in original paper for results on 1 mo and 4 mo

^C Estimated from available data

^D Estimated from number of mothers; number of infants not reported

^E This is not an RCT; the supplemented groups were randomized, but not the control (non-supplemented group); data from comparisons between the supplemented groups not reported.

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

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

^A Non-adjusted

Vitamin D and Cardiovascular Disease

Synopsis.

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and incidence of hypertension. One RCT of almost 2700 elderly British who received either vitamin 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 & 11; Figure 6).

Total cardiovascular events.

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

The RCT randomized almost 2700 elderly participants (65-85 years) from the general population in Ipswich, UK (52° N) to vitamin D₃ 100,000 IU every 4 months or placebo.⁴⁴ After 5 years, 36 percent of the participants had a cardiac or cerebrovascular event, but there was no statistically significant difference between those taking vitamin D or placebo. Similar results were found in subgroups of men and women. The RCT was rated quality B primarily due to inadequate verification of outcomes.

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

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

Cardiovascular death.

The British RCT of vitamin D₃100,000 IU every 4 months versus placebo analyzed cardiovascular death as a primary outcome; 8 percent of the participants had cardiovascular deaths within 5 years.⁴⁴ Fewer people taking vitamin D₃ supplements had cardiovascular deaths (RR = 0.84), but this finding was not statistically significant (95 percent CI 0.65, 1.10). Similar results were found in subgroups of men and women.

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

Ischemic heart disease.

The RCT evaluated total ischemic heart disease.⁴⁴ In this elderly British population, 17 percent had an ischemic heart disease event; no effect of vitamin D₃ supplementation was found. Similar results were found in subgroups of men and women.

Ischemic heart disease death.

The RCT evaluated total ischemic heart disease death as a primary outcome.⁴⁴ In the trial, 3.4 percent had an ischemic heart disease event; no effect of vitamin D₃ supplementation was found (RR = 0.84 [95 percent CI 0.56, 1.27]). Similar results were found in subgroups of men and women.

Myocardial infarction.

In one small analysis, 755 elderly (age 65 to 99 years) Finnish men and women, regardless of cardiovascular history, were evaluated on the basis of myocardial infarction (methodological quality C due to lack of reporting of relevant data including information on the serum 25(OH)D or 1,25(OH)₂D concentrations within the tertiles).⁴⁸ During 10 years of followup, 17 percent of the participants had a myocardial infarction. Both analyses of serum 25(OH)D and 1,25(OH)₂D concentrations found no significant association with risk of myocardial infarction.

Stroke.

The RCT evaluated total cerebrovascular disease.⁴⁴ In this elderly British population, 7.7 percent had a cerebrovascular event; no effect of vitamin 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 followup, 9.3 percent of the participants had a stroke. Both analyses of serum 25(OH)D and 1,25(OH)₂D concentrations found no significant association with risk of stroke.

Cerebrovascular death.

The RCT evaluated cerebrovascular disease death as a primary outcome.⁴⁴ In the trial, 2.0 percent had a fatal stroke; no effect of vitamin D₃ supplementation was found. Similar results were found in subgroups of men and women.

Findings per vitamin D concentration.

The RCT 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).⁴⁵ The risk of cardiovascular events rose below 37 to 50 nmol/L serum 25(OH)D concentration. The Finnish cohort did not report the range of serum 25(OH)D and 1,25(OH)₂D concentrations.⁴⁸

Findings per age and sex.

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

Findings by life stage.

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

- **Postmenopause** Only the RCT provided data on a subgroup that included only postmenopausal women. No effect of vitamin D₃ supplementation was found.
- **Pregnant & lactating women** Not reviewed

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|--|--|--|---|--|
| Trivedi 200 ⁴⁴ Ipswich, UK (52°N) [12609940] | <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

| Author Year Study Name [PMID] | Age Range, Sex (Subgp) | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|---|---------------------------------|----------------|-------|--------------------|---|------------|-------------------------------|-----------------------------------|-------------------|------------|----------|------------------|
| Trivedi 200 ⁴⁴ [12609940] | 65-85 y, Both | CVD, total | 2° | 5 y | Vit D ₃ 100,000 IU every 4 mo | 477 | 1345 | Age adj RR (Vit D/Placebo) | 0.90 ^A | 0.77, 1.06 | 0.22 | B |
| | | | | | Placebo | 503 | 1341 | | | | | |
| | | IHD, total | 2° | Vit D ₃ | 224 | 1345 | Age adj RR (Vit D/Placebo) | 0.94 ^A | 0.77, 1.15 | 0.57 | | |
| | | | | Placebo | 233 | 1341 | | | | | | |
| | | CeVD, total | 2° | Vit D ₃ | 105 | 1345 | Age adj RR (Vit D/Placebo) | 1.02 ^A | 0.77, 1.36 | 0.87 | | |
| | | | | Placebo | 101 | 1341 | | | | | | |
| | | CVD death | 1° | Vit D ₃ | 101 | 1345 | Age adj RR (Vit D/Placebo) | 0.84 ^A | 0.65, 1.10 | 0.20 | | |
| | | | | Placebo | 117 | 1341 | | | | | | |
| | | IHD death | 1° | Vit D ₃ | 42 | 1345 | Age adj RR (Vit D/Placebo) | 0.84 ^A | 0.56, 1.27 | 0.41 | | |
| | | | | Placebo | 49 | 1341 | | | | | | |
| | | CeVD death | 1° | Vit D ₃ | 28 | 1345 | Age adj RR (Vit D/Placebo) | 1.04 ^A | 0.61, 1.20 | 0.89 | | |
| | | | | Placebo | 26 | 1341 | | | | | | |

^A Similar results for subgroups of men and women

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Specific CVD Outcomes | | |
|--|--|---------------------------------|---|---|---|----------------|---------|-------------|-----------|-----------------------------|---|--------------------------|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Wang 2008 ⁴⁵ Framingham Offspring Framingham, MA (mostly) (42°N) [18180395] | <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) All | Outcome stratified by 2 or 3 categories | X ^A | X | X | X | X ^A | X | CVD event |
| Giovannucci 2008 ⁴⁶ HPFS US (various) [18541825] | <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 ⁴⁷ 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) All (even distribution) | Outcome stratified by 4 categories | X | X | X | X | X | X | CVD death |
| Marniemi 2005 ⁴⁸ 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) All | Outcome stratified by tertiles | | X | | | | X | MI Stroke |

^A Not in 3-category analysis

^B Case-control study

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

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

Continued

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

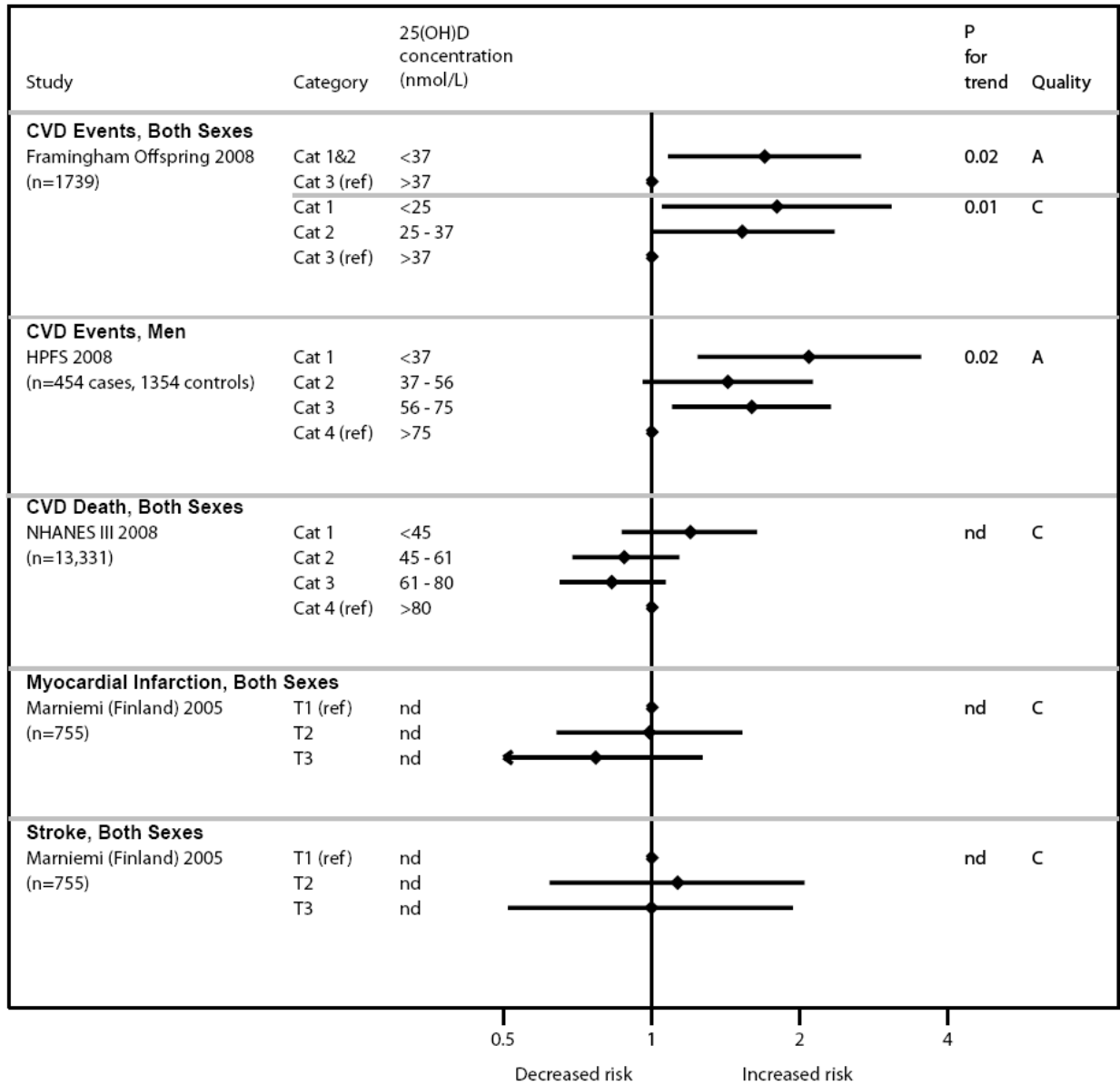
* Statistically significant (P<0.05)

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

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

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

Figure 6. Cardiovascular outcomes risk stratified by vitamin D concentration



Vitamin D and Body Weight

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

Synopsis.

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

Detailed presentation (Tables 12 & 13).

Three RCTs of vitamin D reported body weight (or body mass index [BMI]) as an outcome. The Kuopio (Finland) Osteoporosis Risk Factor and Prevention Study (Kuopio ORFPS) included postmenopausal women in a four-arm study.⁴⁹ Two of the study arms included hormone replacement treatment and are not further discussed here. The remaining two arms compared vitamin 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.⁵⁰ 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.⁵¹ 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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|--|---|---|--|
| Heikkinen 1997 ⁴⁹ Kuopio ORFPS Kuopio, Finland (63°N) [9405029] | <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 ⁵⁰ 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 ⁵¹ 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

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

^A Estimated from reported data

^B Per estimated 95% confidence interval, P=0.17

Vitamin D and Cancer

Cancer from all causes and total cancer mortality.

Synopsis.

No qualified systematic reviews have evaluated relationships between vitamin D and total cancer incidence or mortality. One RCT showed no effect of combined vitamin 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 US) showed no significant association between baseline 25(OH)D concentrations and total cancer mortality.

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

A 4-year population-based RCT,⁵² sampled from a 9 county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin 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 percent CI: 0.38, 1.55). On the hypothesis that cancers diagnosed early in the study would have been present, although unrecognized on entry, the analyses were restricted to women who were free of cancer at 1 year intervention. The relative risk of developing cancer at the end of study for the vitamin D₃ plus calcium group changed to 0.55 (95 percent 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).⁴⁴ Total cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin D₃ supplementation had no significant effect on the prevention of total cancer mortality (HR 0.86; 95 percent CI 0.61, 1.20) or incidence (HR 1.09; 95 percent CI 0.86, 1.36). This trial was rated B because it did not report in sufficient detail the randomization method, and the outcome ascertainment was based on death certificates or self-reported data, not verified with another objective documents (e.g., medical records or pathology reports).

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

Findings by age, sex and/or ethnicity.

There were no differences in the total cancer mortality and incidence between men and women, reported in a 5-year RCT compared the effects of supplemental vitamin 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 percent CI 0.83 to 1.78; ≥100 nmol/L: RR = 1.35; 95 percent CI 0.78 to 2.31; P for trend=0.08]. However, this relationship was not seen in women (P for trend=0.12).⁵³ When racial/ethnic groups were considered separately, there was also no association between baseline 25(OH)D concentrations and total cancer mortality in non-Hispanic whites (P for trend=0.80), non-Hispanic blacks (P for trend=0.14), or Mexican Americans (P for trend=0.37).

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** Analyses using NAHANES III data showed no significant association between baseline 25(OH)D concentrations and total cancer mortality. NHANES III included participants mostly within this life stage.
- **51 – 70 y** A proportion of participants in NHANES III were in this life stage, but no unique conclusions are possible for this life stage separate from those for people 19 to 50 years.
- **≥71 y** One RCT included elderly men and women mostly in this life stage. The trial found no difference in total cancer mortality or incidence between supplemental vitamin D₃ (100,000 IU every 4 months) and placebo.
- **Postmenopause** 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: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments | |
|---|--|--|--|--|--|--|
| Lappe 2007 ⁵² Nebraska, US (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 ⁴⁴ 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% |

^A No difference between the vitamin D and the placebo arm.

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|--|---|--|--|---|---------|---------|-------------|-----------|----------|---|--|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Cohort | | | | | | | | | | | | |
| Freedman 2007 ⁵³ NHANES III US (various) [16481636] | <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 ⁴⁷ 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 | |

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

| Author Year Study Name Location (Latitude) [PMID] | Life Stage | Outcome | 1°/2° | Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|--|------------------------------|--|-------|----------------|--|------------|------------|-----------------------------------|--------|---------------|----------|------------------|
| Lappe 2007 ⁵² Nebraska, US (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 ⁴⁴ [12609940] | 65-85 y, Both sexes | Incident cancer (all causes) | 2° | 5 | Vit D ₃ 100,000 IU every 4 mo (~833 IU/d) | 188 | 1345 | HR (Vit D vs placebo) | 1.09 | 0.86, 1.36 | NS | B |
| | | | | | Placebo | 173 | 1341 | | | | | |
| | | Total cancer mortality | 2° | 5 | Vit D ₃ 100,000 IU every 4 mo (~833 IU/d) | 63 | 1345 | HR (Vit D vs placebo) | 0.86 | 0.61, 1.2 | NS | |
| | | | | | Placebo | 72 | 1341 | | | | | |

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

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

* Statistically significant (P<0.05)

Prostate cancer.

Synopsis.

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

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

A total of 12 nested case-control studies in 14 publications reported on the association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.⁵³⁻⁶⁶ The number of cases ranged from 61 to 749. The latitudes of the studies ranged from 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.

19-50 years.

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

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

51-70 years.

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

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

1,25(OH)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.^{59,62,63,66} 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).⁵⁸ When stratified by age and race, this association was only found in men above the median age of 57 years at time of blood drawn but not in younger men; the association was similar in black and white men.

Findings by life stage.

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

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

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

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

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

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

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

^A For prevention of recurrence of non-melanoma skin cancer

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

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

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

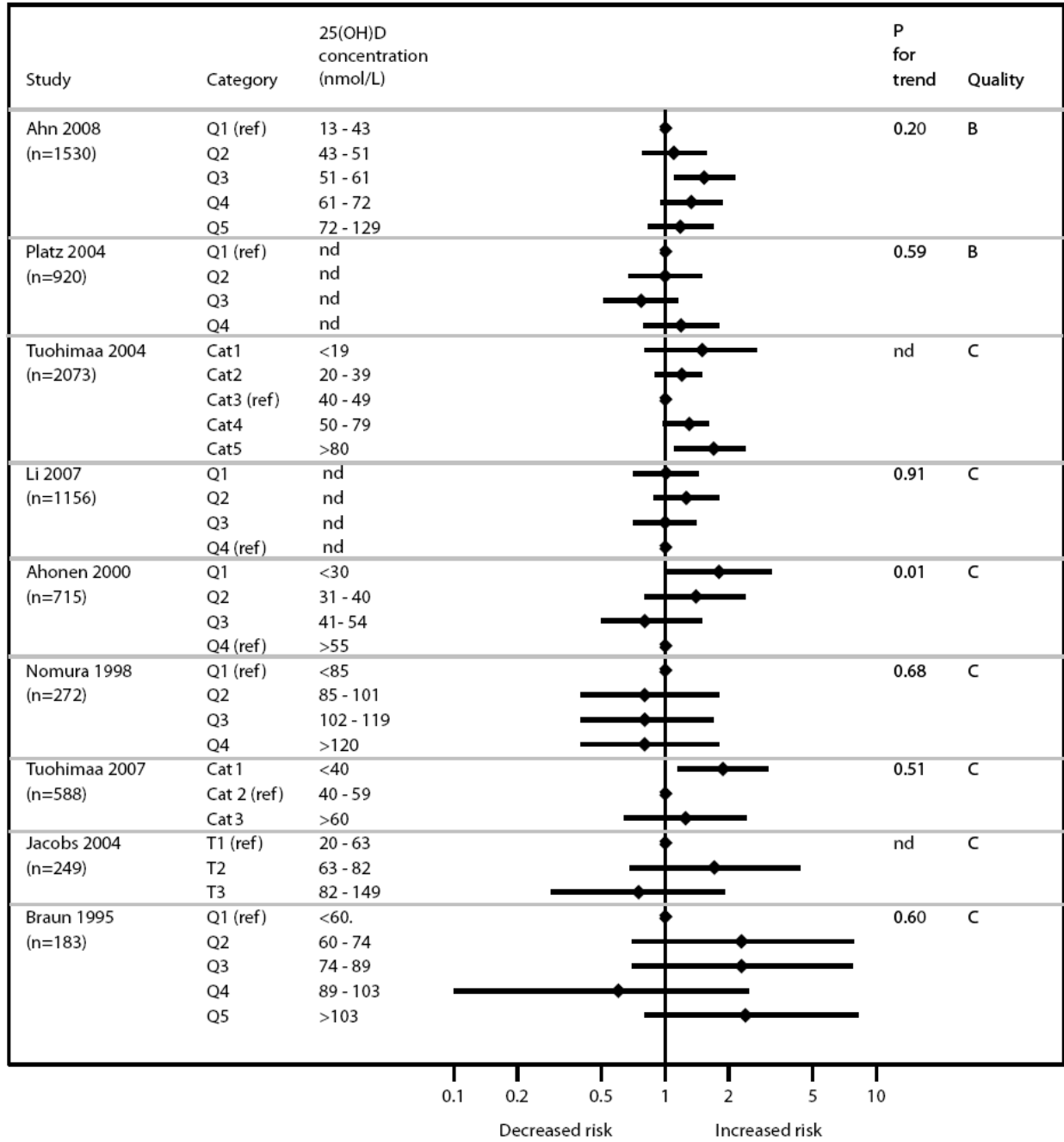
continued

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

*Statistically significant (P<0.05)

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

Figure 7. Prostate cancer risk stratified by vitamin D concentration



Colorectal cancer.

Synopsis.

No qualified systematic reviews have evaluated the association between 25(OH)D concentrations and colorectal cancer mortality or incidence. One B quality RCT of elderly population reported no significant difference in colorectal cancer mortality or incidence between supplemental vitamin 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).

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).⁴⁴ Colorectal cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin 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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|--|---|--|--|
| Trivedi 2003 ⁴⁴ Oxford, UK (52°N) [12609940] | <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% |

CVD = cardiovascular disease; HRT = hormone replacement therapy.

^A No difference between the vitamin D and the placebo arm.

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

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

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

A total of seven nested case-control studies evaluated the associations between 25(OH)D concentrations and risk of colorectal cancer⁶⁷⁻⁷¹ or colon cancer.^{72,73} The number of pairs of cases and controls in these studies ranged from 101 to 588. Another cohort study comprising 16,818 adult community volunteers from the NHANES III⁵³ assessed the association between 25(OH)D concentrations and colorectal cancer mortality. The mean age of the subjects ranged from 44 to 66 years. Locations of the studies ranged from 20° N to 60° N. Baseline 25(OH)D concentrations ranged from 10 nmol/L to 227.5 nmol/L. No studies reported followup 25(OH)D concentrations. Time between blood drawn and the diagnosis of colorectal cancer incidence or mortality ranged from less than 1 year to 17 years. None of the studies reported power calculations. Methodological quality of five nested case-control studies⁶⁷⁻⁷¹ were rated B and two were rated C.^{72,73} Common reasons for downgrading the quality ratings included exclusion of participants without available blood samples, no verification of cancer diagnosis, and lack of adequate statistical adjustments. The cohort study⁵³ 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 III⁵³ analyzed data for both sexes combined. An adjusted analysis found an inverse association between 25(OH)D concentrations and the risk of colorectal cancer mortality (HR: 0.28, highest [≥ 80 nmol/L] compared to lowest tertile [< 50 nmol/L]; P for trend = 0.02). Two studies from WCC reported colon cancer incidence for both sexes combined.^{72,73} One study reported a significantly lower 25(OH)D concentrations in colon cancer cases than controls (58.9 nmol/L vs. 86.6 nmol/L; $P < 0.001$).⁷³ Both studies reported no significant association between 25(OH)D concentrations and colon cancer risk by trend analysis.

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

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

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

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

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

Findings per special populations.

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

Findings excluding early cases.

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

Findings on 1,25-Dihydroxyvitamin D.

A total of three studies evaluated the associations between 1,25(OH)₂D concentrations and colorectal cancer risk^{67,70} or colon cancer.⁷³ None of the studies found a significant association by trend analysis. One study reported no significant association between 1,25(OH)₂D concentrations and rectal cancer risk.⁶⁷

Findings by life stage.

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

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|--|--|--|--|--|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Cohort | | | | | | | | | | | | |
| Freedman 2007 ⁵³ NHANES III US (various) [16481636] | <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 ⁷³ 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 ⁷⁰ 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 ⁷² 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% |
| Otani 2007 ⁶⁸ 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 quintiles | X | X | X | X | X | X | |

continued

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|---|--|---|--|--|--|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Tangrea 1997 ⁶⁷ ATBC Finland (~60°N) [9242478] | <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 ⁷¹ 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 ⁶⁹ 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% |

^A This table is ordered alphabetically by study author.

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

^C Participants of a hip fracture prevention RCT of vitamin D3 and calcium

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

| Author Year Study Name [PMID] | Life Stage | Outcome (n/N; Incidence) | Followup Duration (Time to Dx) | 25(OH)D Concentration, nmol/L | No. of Cases | No. in Category | Adjusted OR | 95% CI | P for Trend | Study Quality |
|---|--------------------|---|---|-------------------------------------|-------------------------------|--------------------|----------------|-------------|-------------------|------------------|
| Cohort study | | | | | | | | | | |
| Colorectal cancer mortality | | | | | | | | | | |
| Women | | | | | | | | | | |
| Freedman 2007 ⁶³ [17971526] | 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* | | |
| | ≥71 | | | ≥80 | 14 | ~5606 | 0.28 | 0.11, 0.68* | | |
| Nested case-control study | | | | | | | | | | |
| Colorectal cancer | | | | | | | | | | |
| Men | | | | | | | | | | |
| Otani 2007 ⁶⁸ Japan PHC [17622244] | 19-50 | Colorectal cancer (N=196 cases; 392 controls) | 1-13 | <57.2 | 43 | 74 | 1 | Reference | 0.39 | B |
| | 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 | | |
| | | | | ≥80.2 | 44 | 80 | 0.73 | 0.35, 1.5 | | |
| Wu 2007 ⁶⁹ HPFS [17623801] | 19-50 | Colorectal cancer (179 cases; 356 controls) | 1-9 | 46, median | 45 | 71 | 1 | Reference | 0.24 ^B | B |
| | 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 | |
| | | | | 80.0 | 9 | 30 | 0.38 | | 0.12, 1.26 | |
| | | | | 97.0 | 14 | 36 | 0.45 | | 0.15, 1.40 | |
| | | | | 51-70 ^A | Colorectal cancer, age ≥65 | 48.2, median | 34 | | 55 | 1 |
| ≥71 | 66.8 | 36 | 61 | 0.97 | | | 0.50, 1.87 | | | |
| | 80.0 | 19 | 58 | 0.56 | | | 0.27, 1.15 | | | |
| | 97.0 | 27 | 54 | 0.83 | | | 0.39, 1.75 | | | |
| Tangrea 1997 ⁶⁷ ATBC [9242478] | 19-50 | 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 | | |

continued

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

continued

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

continued

| Author Year Study Name [PMID] | Life Stage | Outcome (n/N; Incidence) | Followup Duration (Time to Dx) | 25(OH)D Concentration, nmol/L | No. of Cases | No. in Category | Adjusted OR | 95% CI | P for Trend | Study Quality |
|---|--------------------|--|---|-------------------------------------|-----------------|--------------------|----------------|------------------|----------------|------------------|
| Wu 2007 ⁶⁹ HPFS [17623801] | 19-50 | 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 ⁶⁸ 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 ⁷⁰ 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 | 0.52 | 0.14, 1.93 | | |
| | | | | 92.4 | 10 | 31 | 0.31 | 0.08, 1.31 | | |

* Statistically significant (P<0.05)

^A Most representative life stage.

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

^C Results were not notably changed when cases diagnosed within the first year after blood collection were excluded (P for trend not reported). Subgroup analyses per age were also reported as follows: Age ≥ 60, OR = 0.35 (95% CI 0.14, 0.87) between the lowest and highest quintiles; P for trend = 0.006. Age < 60, OR = 1.36 (95% CI 0.48, 3.92) between the lowest and highest quintiles; P for trend = 0.70.

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

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

^F P for trend = 0.04 when cases diagnosed within 2 years of blood collection were excluded.

Figure 8. Colorectal cancer risk stratified by vitamin D concentration

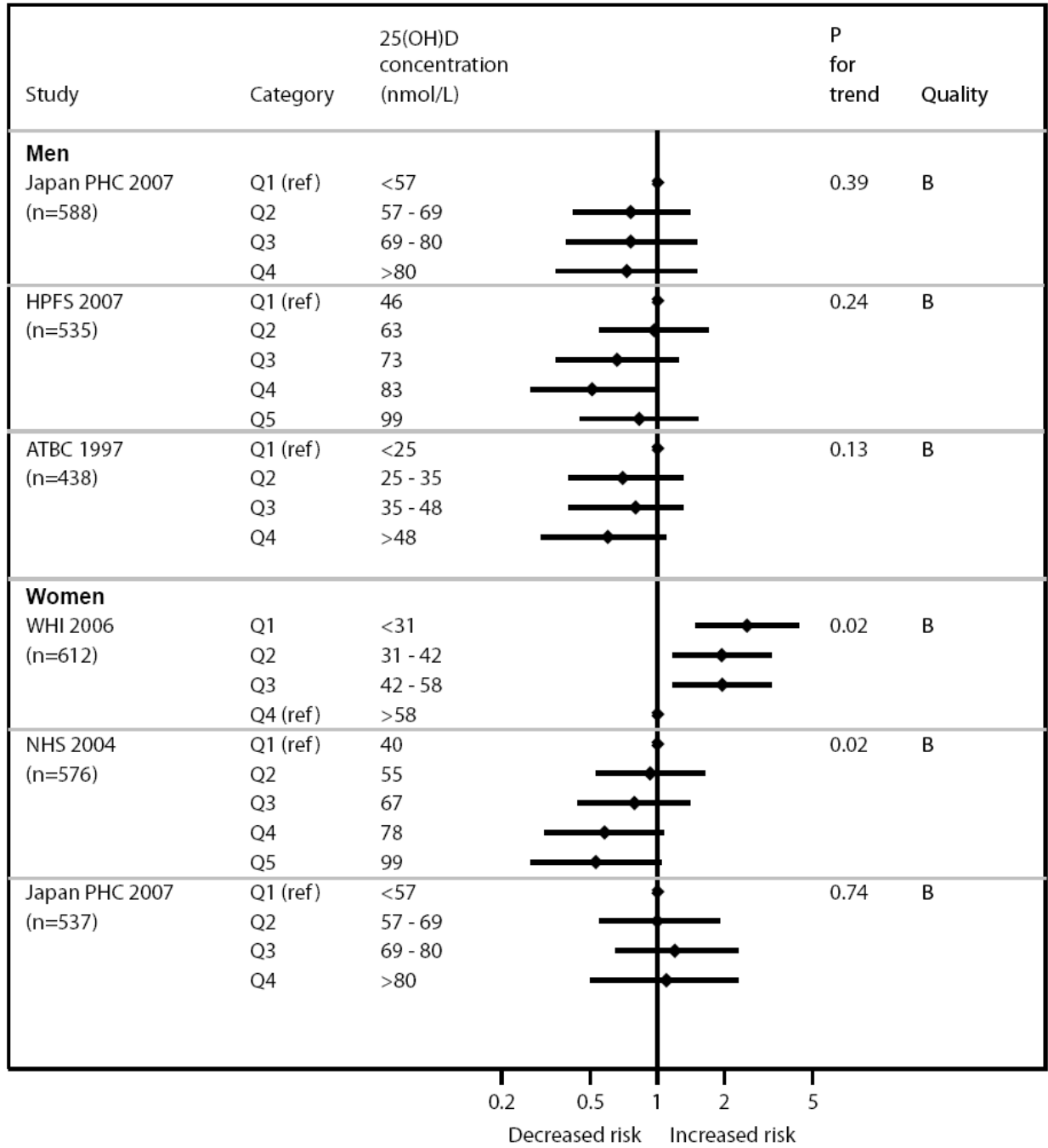


Figure 9. Colon cancer risk stratified by vitamin D concentration

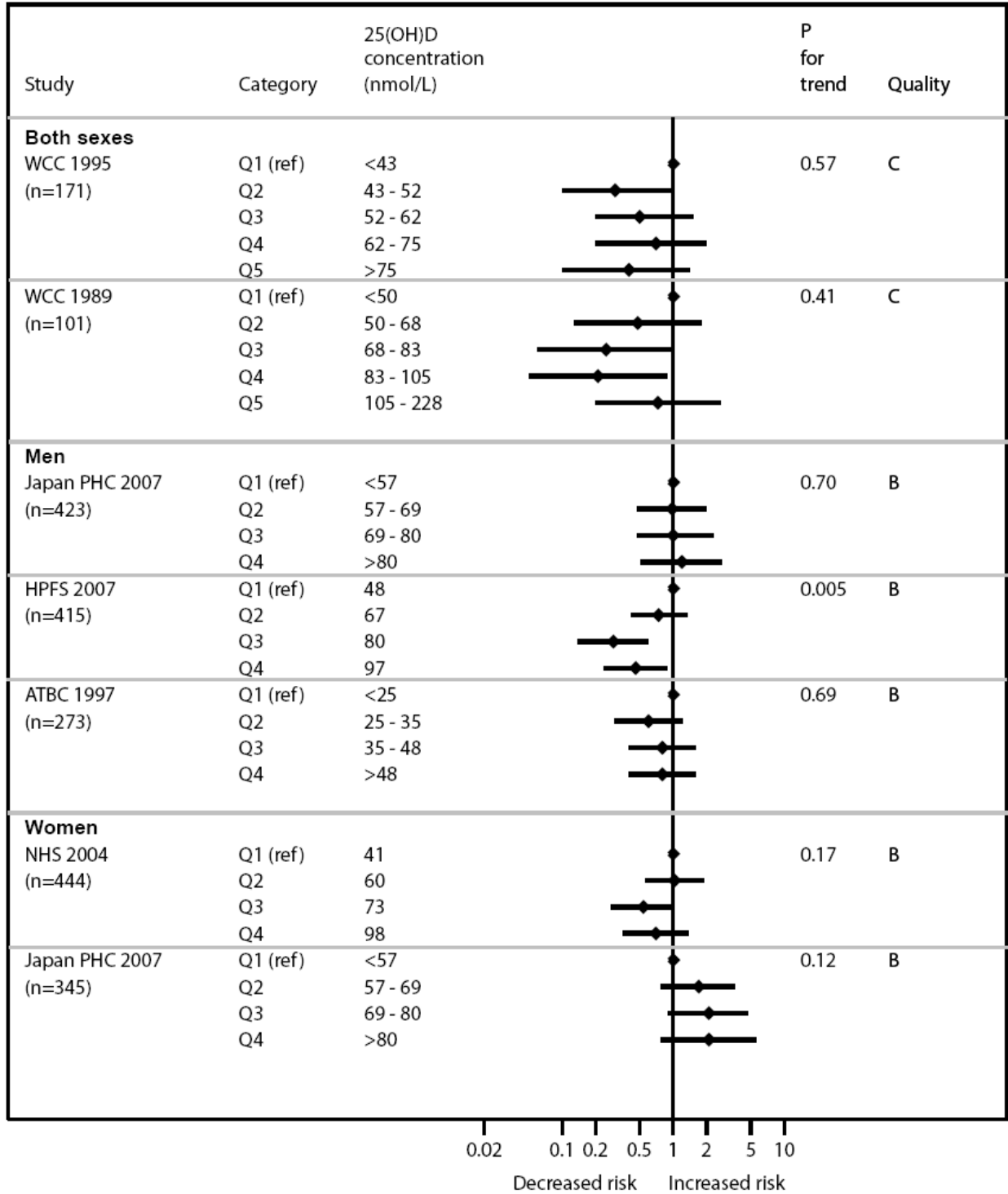
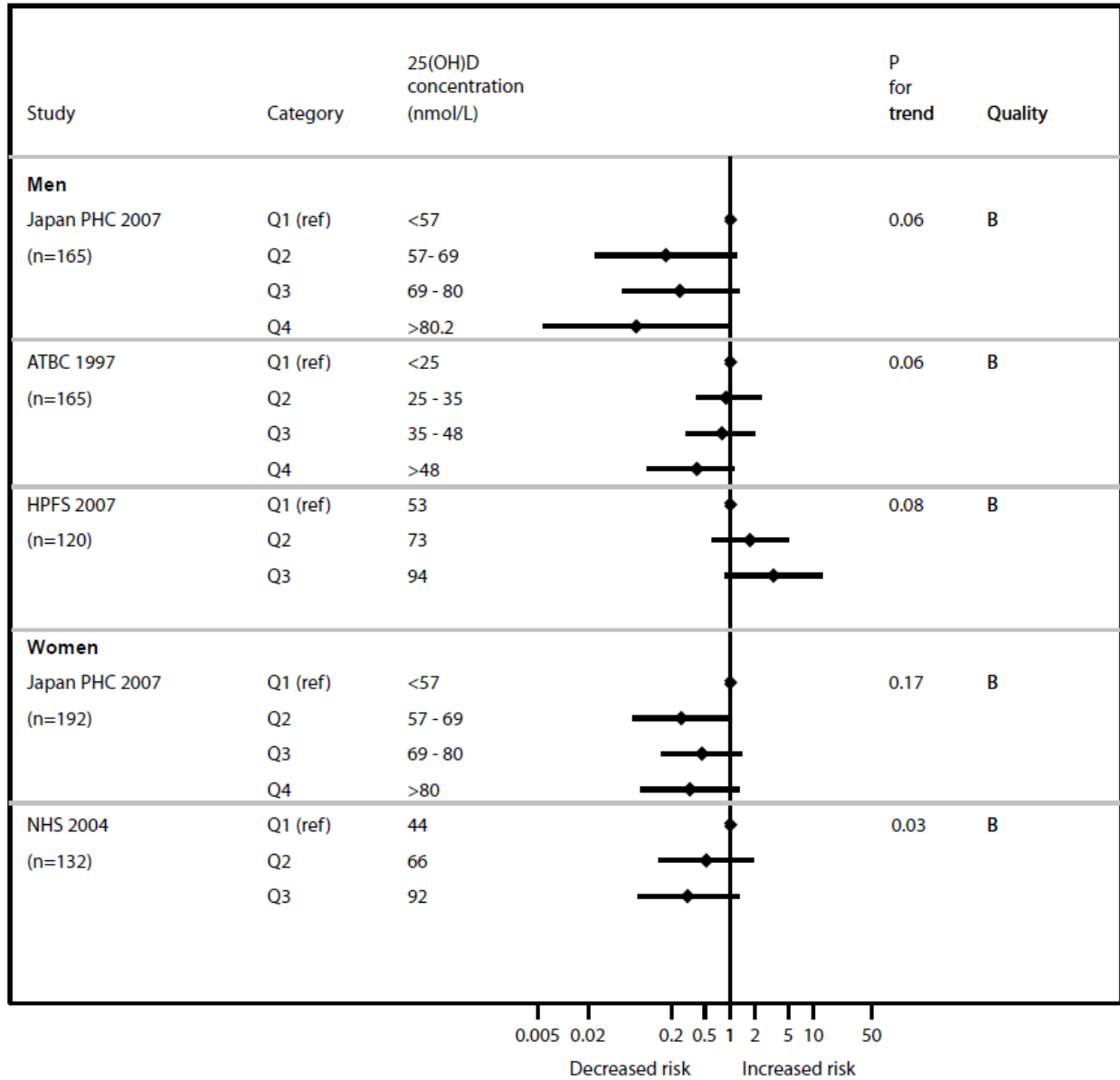


Figure 10. Rectal cancer risk stratified by vitamin D concentration



Colorectal adenoma.

Synopsis.

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

Detailed presentation (Tables 24 & 25).

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

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Comments | | | |
|--|---|----------------------------|--|--|--|---------|---------|-------------|----------|-----------|---|--|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | | Lifestyle | | |
| Nested case-control | | | | | | | | | | | | |
| Platz 2000 ⁷⁴ NHS US (various) [11045788] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | Any 59 (7) 0 | <ul style="list-style-type: none"> • Assay method • Season blood drawn | RIA (Horris 1993) All | <ul style="list-style-type: none"> • Colorectal adenoma risk stratified by baseline 25(OH)D quartiles | X | X | X | X | X | X | Aspirin user: 26%; Hormone replacement therapy: 36% |

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

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

* Statistically significant (P<0.05)

^A Most representative life stage

Breast cancer.

Synopsis.

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

Detailed presentation (Tables 26 & 27).

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

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

Findings by age and sex.

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

Findings by life stage.

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

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | |
|---|---|----------------------------------|--|--|---|---------|---------|-------------|-----------|----------|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Cohort | | | | | | | | | | | |
| Freedman 2007 ⁵³ NHANES III US (38° N) [17971526] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | Non-institutionalized 44 (ND) | <ul style="list-style-type: none"> • Assay method • Season blood drawn | RIA All year | Breast cancer risks: Quintile 1 vs. Quintile 2 | X | X | X | | X | X |
| Nested Case-Control | | | | | | | | | | | |
| Bertone-Johnson 2005 ⁷⁵ NHS US (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 | X | | X |
| Freedman 2008 ⁷⁶ 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 | X | | X |

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

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

continued

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

* Statistically significant (P<0.05)

^A Total number of women not reported

Pancreatic cancer.

Synopsis.

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

Detailed presentation (Tables 28 & 29).

51 - 74 years.

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

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

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

Findings by life stage.

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

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

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

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

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

* Statistically significant (P<0.05)

Vitamin D and Immunologic Outcomes

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

Synopsis.

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

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

Detailed presentation (Tables 30 & 31).

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

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

Findings by life stage.

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

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

| Author Year | Study Name | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | |
|---|---|---|--|---------------------------|---|-----------|---------|---------|-------------|-----------|----------|------------|
| | | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Melamed 2008 ⁴⁷ NHANES III US (various) [18695076] | <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 ⁴² 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 31. Vitamin D (mother) and immunologic outcomes (offspring): Results of cohort studies

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

^A Crude OR

Vitamin D and Pregnancy-related Outcomes

Preeclampsia.

Synopsis.

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

Detailed presentation (Tables 32 & 33).

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

Findings by life stage.

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

Other outcomes.

Synopsis.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | | |
|--|---|-------------------------------|--|--|---|---------|---------|-------------|-----------|--|--|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Bodnar 2007 ⁹ 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 | | | |

^A Pregnancy Exposures and Preeclampsia Prevention Study

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

| Author Year Study Name Location (Latitude) [PMID] | Life Stage | Outcome (n/N; Incidence) | Followup Duration (Time to Dx) | Vit D Measure | Concentration, nmol/L | No. of Cases | No. in Category | Adjusted OR | 95% CI | Study Quality |
|---|------------|--|--------------------------------------|----------------------|--------------------------|-----------------|--------------------|----------------|-----------|------------------|
| Bodnar 2007 ^{9A} PEPPS ^B US (41°N) [17535985] | Pregnancy | Preeclampsia (55/1198; 4%) ^C | ND | 25(OH)D ^D | <37.5 (vs. >37.5) | 49 | 265 | 5.0 | 1.7, 14.1 | B |

^A This is a nested case-control study

^B Pregnancy Exposures and Preeclampsia Prevention Study

^C Incidence obtained from the "parent" cohort study in which this case control study is nested.

^D Early in pregnancy, approximately 30 wk before outcome assessment

Vitamin D and Clinical Outcomes of Bone Health

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

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

Rickets.

Synopsis.

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

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

Detailed presentation (Table 34).

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

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

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

Findings by life stage.

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

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

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

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Cranney 2007 ⁶ [18088161] | | |
| Design | Systematic review of RCTs and observational studies | | |
| Population | <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 | <p>Intervention (Exposure):</p> <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) <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 | | |

Fractures, falls, or performance measures.

Synopsis.

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

Findings from three additional RCTs (published after the Ottawa EPC report)⁸⁰⁻⁸² also did not show significant effects of either vitamin 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 35 & 36).

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

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

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

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

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

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

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

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

Additional RCTs published after the Ottawa EPC report.

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

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data
- **51 – 70 y** The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report
- **≥71 y** Findings from three new RCTs did not show significant effects of either vitamin 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** The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report
- **Pregnant & lactating women** Not reviewed

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

| Author Year Study Name Location (Latitude) [PMID] | | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|--|---|--|---|--|----------|
| Lyons 2007 ⁸² South Wales, UK (52°N) [17473911] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | <p>Living in care facilities including some elderly with mobility, cognitive, visual, hearing or communication impairments</p> <p>84 (62-107)</p> <p>23.7</p> | nd | Vit D ₂ 100,000 IU 4-monthly vs. placebo | 80% (percentage of occasions observed to take tablets) | |
| Burleigh 2007 ⁸¹ Scotland (55° 57'N) [17656420] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | <p>Inpatient with high levels of comorbidity, mortality and polypharmacy</p> <p>83 (7.6)</p> <p>40</p> | 25(OH)D: 22.0 nmol/L | Vit D ₃ 800 IU/d + Ca carbonate 1200 mg/d vs. Ca carbonate 1200 mg | Ca group=87%, Vit D+Ca group=89% (total study drug taken/total study drug prescribed, as recorded in drug prescription charts) | |
| Bunout 2006 ⁸⁰ Chile (32°S) [16797903] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | <p>Healthy</p> <p>76 (4)</p> <p>11.6</p> | 25(OH)D: ≤40 nmol/L | Ca 800 mg/d vs. Ca 800 mg/d + Vit D 400 IU/d (with and without exercise training) | 92% (tablet counting) | |

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

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|--|----------------------|-------------------|-------|---|---|-----------------|------------|-----------------------------------|--------|------------|----------|------------------|
| Lyons 2007 ^{B2} [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 ^{B1} [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 ^{B0} [16797903] | ≥71 both sexes | Fall | 2° | 9 mo | Ca 800 mg | 13 ^B | 24 | Fall free survival curve | nd | | NS | C |
| | | | | | Ca 800 mg + exercise training | 6 ^B | 22 | | | | | |
| | | | | | Vit D 400 IU + Ca 800 mg | 9 ^B | 24 | | | | | |
| | | | | | Vit D 400 IU + Ca 800 mg + Exercise training | 8 ^B | 22 | | | | | |

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

^B Estimated from figure

Vitamin D and all-cause Mortality

Synopsis.

This synopsis is based on our reanalysis of a systematic review of RCTs on vitamin D supplementation for mortality.¹ In addition, it summarizes four observational studies on the association of vitamin D and all-cause mortality.

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

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

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

Detailed presentation (Tables 37, 38 & 39).

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

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

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

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

¹ Numerical data were extracted from previous systematic reviews –no additional studies were identified. For this reason, we did not appraise studies for their methodological quality.

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

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Autier 2007 ⁸³ [17846391] | | |
| Design (Search Years) | Randomized controlled trials (1992-2006) | | |
| Population | Community dwelling or institutionalized adults | | |
| Intervention (Exposure) and Comparator | Supplementary vitamin D (at least 1000 mg/d) without calcium vs. placebo or no treatment | | |
| Results | 18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (\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. | | |
| Comments | See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail. | | |
| AMSTAR Criteria | | | |
| A priori design? | Yes | Study quality assessment performed? | No |
| Two independent reviewers? | No | Study quality appropriately used in analysis? | NA |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | No |
| Included and excluded studies listed? | No | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores) | |

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

Lyons 2007 (n=3343, 24 percent males) used monthly supplementation with 100,000 IU of vitamin D₂, orally for 3 years.⁸² The trial took place in South Wales (latitude ~52°N) and included older people (mean age 84 y) living in sheltered accommodation. The primary outcome was prevention of fractures. The Lyons 2007 RCT received grade “C” for the all-cause mortality outcome, because of inconsistencies in the reported data. This RCT is included in the reanalysis described below.

Reanalysis.

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

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

Overall, there were no significant effects of vitamin D supplementation on mortality. The RR was 0.97 (95 percent CI 0.92, 1.02), with no evidence for between-study heterogeneity (P=0.39, I²=0 percent).

Cohort studies.

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

Table 39 summarizes the findings of the four studies. Briefly, only Jia 2007⁹⁰ 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 2008⁴⁷ performed analyses in subgroups of men and women, and <65 or ≥65 years of age, and found no significant associations (Table 33).

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | | |
|---|--|---|--|--|--|---------|---------|-------------|-----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Jia 2007 ⁹⁰ UK (57°N) [17442130] | <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 |
| Shambrook 2004 & 2006 ^{91,92} 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 ⁹³ 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 ⁴⁷ 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 |

^A Fracture Risk Epidemiology in the Elderly

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

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

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

continued

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

^A Fracture Risk Epidemiology in the Elderly

^B Per unit change in the log-transformed concentration.

Vitamin D and Hypertension and Blood Pressure

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

Hypertension.

Synopsis.

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

Detailed presentation (Tables 40 & 41).

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

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

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

Findings per vitamin D concentration.

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

Findings per age and sex.

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

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Vitamin D Concentration | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | |
|--|---|---|--|--|--|---------|---------|-------------|-----------|----------|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Forman 2007 ⁹⁴ HPFS, NHS US (various) [17372031] | <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 ⁹⁵ 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 | |

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

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

* Statistically significant (P<0.05)

^A Due to formatting error in study table, no data on numbers of women in each category.

Vitamin D and blood pressure.

Synopsis.

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

Detailed presentation (Tables 42 & 43).

The A quality trial of single-dose vitamin D, performed in Cambridge, UK, recruited older adults (63 to 76 years, mean 70 years) who were not taking antihypertensive medications.⁹⁶ During the winter, they were given either a one-time dose of vitamin 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.⁹⁷ 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.⁵¹ The men who received the vitamin D supplements had a net increase in systolic blood pressure of 4 mm Hg, which was close to statistically significant (P=0.06), but no significant difference in diastolic blood pressure. The study was limited by a high dropout rate (26 percent).

Findings per intake level.

No conclusions can be reached about an intake level threshold. In individual trials, a single dose of 100,000 IU of cholecalciferol had no significant effect on systolic and diastolic blood pressure after 5 weeks, a daily dose of vitamin 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. The study of older women found a significant decrease in systolic blood pressure with relatively low dose

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** A single study of men in this life stage found a near significant increase in systolic blood pressure with vitamin D and no effect on diastolic blood pressure.
- **51 – 70 y** One trial included people with an average age of 70 years, implying that about half were within this life stage. No significant effect on blood pressure was found of a single large dose of vitamin D.
- **≥71 y** Both trials included people within this life stage. The trial of people with an average age of 70 years found no significant effect of a single large dose of vitamin D. The single trial of women over age 70 years found a significant benefit for systolic blood pressure for vitamin D₃ 800 IU and calcium carbonate 1200 mg compared with calcium carbonate 1200 mg alone.
- **Postmenopause** The women in both trials were postmenopausal. See the ≥71 y life stage.
- **Pregnant & lactating women** Not reviewed

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|--|--|--|--|
| Scragg 1995 ⁹⁶ Cambridge, UK (52°N) [7498100] | <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 ⁹⁷ 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 ⁵¹ 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 43. Vitamin D and blood pressure: Results of RCTs

| Author Year Study Name [PMID] | Age Range, Sex | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|---|----------------------|---------|-------|------------------|---|-----------------|----------|----------|--------|-------------------------|-------------|--------------------------|----------|------------------|
| SYSTOLIC BLOOD PRESSURE | | | | | | | | | | | | | | |
| Scragg 1995 ⁹⁶ UK [7498100] | 63-76 y, Both | SBP | 1° | 5 wk | Vit D ₃ 100,000 IU (2.5 mg), 1 dose | 95 | mm Hg | 149 | -5 | -14.4, 4.4 ^A | 0 | -4.2, 4.2 ^A | 0.81 | A |
| | | | | | Placebo | 94 | | 147 | -5 | -17.9, 7.9 ^A | | | | |
| Pfeifer 2001 ⁹⁷ Germany [11297596] | 70-86 y, Women | SBP | 1° | 8 wk | Vit D ₃ 800 IU +Ca carbonate 1200 mg | 73 | mm Hg | 144.1 | -13.1 | nd | -7.4 | -13.6, -1.2 ^A | 0.02 | B |
| | | | | | Ca carbonate 1200 mg | 72 | | 140.6 | -5.7 | nd | | | | |
| Nagpal 2009 ⁵¹ New Delhi, India [19125756] | 44 (8, SD) Men | SBP | 2° | 6 wk | Vit D ₃ 120,000 IU every 2 wk | 35 | mm Hg | 124 | +0.6 | -2.7, 3.9 | +4.0 | -0.02, 8.0 | 0.06 | B |
| | | | | | Placebo | 36 | | 124 | -3.4 | -5.8, -1.0 | | | | |
| DIASTOLIC BLOOD PRESSURE | | | | | | | | | | | | | | |
| Scragg 1995 ⁹⁶ UK [7498100] | 63-76 y, Both | DBP | 1° | 5 wk | Vit D ₃ 100,000 IU (2.5 mg), 1 dose | 95 | mm Hg | 82 | -1 | -6.8, 4.8 ^A | 0 | -2.8, 2.8 ^A | 0.92 | A |
| | | | | | Placebo | 94 | | 82 | -1 | -6.8, 4.8 ^A | | | | |
| Pfeifer 2001 ⁹⁷ Germany [11297596] | 70-86 y, Women | SBP | 1° | 8 wk | Vit D ₃ 800 IU +Ca carbonate 1200 mg | 73 | mm Hg | 84.7 | -7.2 | nd | -0.3 | -0.7, -0.1 ^A | 0.10 | B |
| | | | | | Ca carbonate 1200 mg | 72 | | 82.6 | 6.9 | nd | | | | |
| Nagpal 2009 ⁵¹ New Delhi, India [19125756] | 44 (8, SD) Men | SBP | 2° | 6 wk | Vit D ₃ 120,000 IU every 2 wk | 35 | mm Hg | 78 | +0.4 | -2.1, 3.0 | +1.7 | -1.5, 4.9 | 0.31 | B |
| | | | | | Placebo | 36 | | 77 | -1.3 | -3.2, 0.7 | | | | |

^A Estimated from available data

Vitamin D and Bone Mineral Density or Bone Mineral Content

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

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

Synopsis.

The Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents (6 months through 18 years old). Furthermore, Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck in postmenopausal women and elderly men. However, there was discordance between the results from RCTs and the majority of observational studies.⁶ Three new RCTs identify from our updated search all showed no significant effects of vitamin D supplementation on BMC or BMD in children or adults, respectively.

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

Detailed presentation (Tables 44 & 45).

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

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

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

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

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

concentrations and baseline BMD of the lumbar spine, femoral neck and radius. However, only high dose supplementation with 14,000 IU/wk of vitamin 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.⁹⁸ 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 percent; control, +0.2 percent).

One B quality RCT analyzed 89 and 83 healthy adult women and men separately.⁹⁹ The participants were Pakistani immigrants living in the Copenhagen area of Denmark (latitude 55 N°). Women and men were randomly assigned to receive either daily dose of 400 IU or 800 IU vitamin 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.^{35,99} First RCT analyzed 26 healthy girls, who were Pakistani immigrants primarily living in the Copenhagen area Denmark (latitude 55 N°).⁹⁹ Girls were randomly assigned to receive either daily dose 400 IU or 800 IU vitamin 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. Second RCT analyzed 168 healthy girls, living in the Greater

Findings by life stage.

- **0 – 6 mo** The Ottawa EPC report concluded that there is inconsistent evidence for an association between a specific serum 25(OH)D concentration and the bone health outcome BMC in infants. There were no new data since the Ottawa report.
- **7 mo – 2 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **3 – 8 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **9 – 18 y** The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. Two new RCTs enrolled only girls in this life stage. The results showed no significant differences in whole body BMC changes between either lower doses of vitamin D (200 or 400 IU/d) or higher dose of vitamin D (800 or 2000 IU/d) and the placebo groups.
- **19 – 50 y** The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled primarily men and women in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D₃ (400 IU/d or 800 IU/d) and the placebo groups.
- **51 – 70 y** The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled some men in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin 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** There were no new data since the Ottawa report.
- **Pregnant & lactating women** There were no new data since the Ottawa report.

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

| Author Year Study Name Location (Latitude) [PMID] | | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|--|--|--|---|---|---|
| Zhu 2008 ⁹⁸ Perth, Australia (32 °S) [18410225] | <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 ⁹⁹ 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 ³⁵ 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 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report

| Author Year Study Name Location (Latitude) [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, mo | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|---|---|------------------------|-------|-------------------------|---|--------------------|--------------------|----------|--------|------------------|-------------|------------------------|----------|------------------|
| Zhu 2008 ⁹⁸ Perth, Australia (32 °S) [18410225] | 71+. Women only | Hip BMD | 1° | 12 | Vit D ₂ 1000 IU + Ca citrate 1200 mg | 123 | mg/cm ² | 851 | 0.5% | -0.09, 1.09 | 0.3% | nd | NS | A |
| | | | | | Ca citrate 1200 mg | 133 | | 826 | 0.2% | -0.19, 0.59 | | | | |
| Andersen 2008 ⁹⁹ Copenhagen, Denmark (55 N°) [18208636] | 18-53, Women only | Lumbar spine BMD | 1° | 12 | Vit D ₃ 400 | 30/21 ^A | mg/cm ² | 1.06 | 0% | nd | -1% | nd | NS | B |
| | | | | | Vit D ₃ 800 | 30/21 | | 0.98 | 1% | nd | 0% | nd | NS | |
| | | | | | Placebo | 29/18 | | 0.99 | 1% | nd | | | | |
| Andersen 2008 ⁹⁹ Copenhagen, Denmark (55 N°) [18208636] | 18-64, Men only | Lumbar spine BMD | 1° | 12 | Vit D ₃ 400 | 25/19 ^A | mg/cm ² | 1.03 | 2% | nd | 0% | nd | NS | B |
| | | | | | Vit D ₃ 800 | 31/26 | | 0.92 | 7% | nd | 5% | nd | NS | |
| | | | | | Placebo | 27/19 | | 1.03 | 2% | nd | | | | |
| Andersen 2008 ⁹⁹ Copenhagen, Denmark (55 N°) [18208636] | 10-15 y girls | BMC | 1° | 12 | Vit D ₃ 400 | 9/7 ^A | kg | 1.3 | 22% | nd | 7% | nd | NS | C ^B |
| | | | | | Vit D ₃ 800 | 9/7 | | 1.5 | 10% | nd | -5% | nd | NS | |
| | | | | | Placebo | 8/7 | | 1.7 | 15% | nd | | | | |
| El-Hajj 2006 ³⁵ Beirut, Lebanon (33°N) [16278262] | 10-17 y girls | BMC | 1° | 12 | Vit D 2000 IU | 55 | kg | 1.2 | 6.2% | 4.7, 7.7 | 0.1% | -1.1, 2.0 ^C | NS | C |
| | | | | | Vit D 200 IU | 58 | | 1.1 | 6.1% | 4.6, 7.6 | 1.1% | -0.8, 3.2 ^C | NS | |
| | | | | | Placebo | 55 | | 1.1 | 5.0% | 3.8, 6.2 | | | | |
| | Subgroup– Premenarcheal girls, mean age 10 y | BMC | 1° | 12 | Vit D 2000 IU | 14 | kg | 0.8 | 11.6% | 9.4, 13.8 | 4.2% | 0.7, 7.7 ^C | NS | |
| | | | | | Vit D 200 IU | 12 | | 0.7 | 11.4% | 9.1, 13.7 | 4.0% | 0.5, 7.5 ^C | NS | |
| | | | | | Placebo | 8 | | 0.8 | 7.4% | 4.7, 10.1 | | | | |

^A Baseline/final sample size

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

^C Estimated from available data

Calcium and Health Outcomes

Calcium and Growth

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

Synopsis.

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

Detailed presentation (Tables 46, 47 & 48).

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

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

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

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

Findings by life stage.

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

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

| | | | |
|--|---|---|-----|
| Author Year [PMID] | Winzenberg 2007 ¹⁰⁰ [17636098] | | |
| Design (Search Years) | Randomized controlled trials (1966-2005) | | |
| Population | Children <18 y | | |
| Intervention (Exposure) and Comparator | Supplemental and dietary calcium 300-1200 mg/d vs. placebo | | |
| Results | 17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity | | |
| Comments | Post hoc analysis performed on trials identified for a meta-analysis of randomized controlled trials of calcium on bone outcomes | | |
| AMSTAR | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | No | Publication bias assessed? | Yes |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No |
| Study characteristics provided? | Yes | Unclear if all languages included; study quality assessed but not factored into the M-A | |

Table 47. Calcium and growth: Characteristics of primary studies

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | |
|---|---|--|---|--|-----------|---------|---------|-------------|-----------|----------|--|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | |
| Lorenzen 2006 ¹⁰¹ Denmark (55°N) [16400044] | <ul style="list-style-type: none"> Health status Mean age (range/SD), y Male (%) | no specific health issue reported 13 0 | 88-item FFQ (no internal validation); dietary calcium: 957 mg/d; 25(OH)D: 34.5 nmol/L | Ca CO ₃ (Ca 500 mg/d) X 1 y vs. placebo | x | x | x | | | | RCT; Danish surnames only |
| Lappe 2004 ¹⁰² Omaha, NE US (41°N) [15354150] | <ul style="list-style-type: none"> Health status Mean age (range/SD), y Male (%) | healthy 9.5 0 | 3-d food record (no internal validation); dietary intake calcium: 819 mg/d; dietary vit D 180 IU/d (4.5 µg/d) | Calcium rich diet (~1656 mg/d) vs. usual diet (~961 mg/d); wt & ht change at 2 y | x | x | x | | | x | Post hoc of RCT on bone mass; 95% white, 5% black |
| Johnson 1994 ¹⁰³ Washington DC, US (38°N) [8201444] | <ul style="list-style-type: none"> Health status Mean age (range/SD), y Male (%) | pregnant; no DM, sickle, thalassemia, HbC disease 22 (39% 16-19) 0 | FFQ (no internal validation); calcium 933.4 mg/d | Relationship between maternal calcium intake and birth weight, height | | | | | | | Cohort study; all African American; Total Ca (from food) |

Table 48. Calcium and growth: Results of primary studies

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

^A Estimated from reported data

Calcium and Cardiovascular Disease

Synopsis.

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

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

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

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

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

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

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

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

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

Cardiovascular death.

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

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

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

Cardiac events, total.

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

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

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

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

Cardiac death.

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

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

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

Cardiac events, nonfatal.

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

Stroke, total.

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

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

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

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

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

Stroke death.

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

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

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

Findings per calcium intake level.

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

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

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

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

Findings per age and sex.

The majority of studies (and the large majority of individuals) included mostly people between the ages of about 40 and 70 years. The youngest individuals included were 32 year old women in the NHS. Apparently very few individuals were over the age of 70 years. Only a small Finnish study (Marniemi 2005⁴⁸) restricted the study cohort to only older adults (65 years and older). This study found no significant associations between calcium intake and cardiovascular events. No study reported a subgroup analysis based on age. The reported data do not allow further conclusions based on age.

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

Findings by life stage.

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

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Specific CVD Outcomes | | | |
|--|--|------------------------------------|---|--|---|---------|---------|-------------|--------------------------|-----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | | Lifestyle | | |
| Al-Delaimy 2003 ¹⁰⁷ HPFS US (various) [12663277] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | No CVD 54 (9) 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Outcome stratified by total Ca intake quintiles | X | X | X | X | | X | IHD MI Cardiac death Total Ca (both) |
| Ascherio 1998 ¹⁰⁹ HPFS US (various) [9743511] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No CVD nd (40-75) 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Outcome stratified by total Ca intake quintiles | X | X | X | X | | X | Stroke Total Ca (both) |
| Bostick 1999 ¹¹⁰ Iowa WHS Iowa (42°) [9921960] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No IHD 61 (55-69) 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Outcome stratified by total Ca intake quartiles | X | X | X | X | | X | Cardiac death Total Ca (both) |
| Iso 1999 ¹¹¹ NHS US (various) [10471422] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No CVD 46 (32-57) 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | | X | | | | X | Stroke Total Ca (food) |
| Larsson 2008 ¹¹² ATBC SW Finland (~60°N) [18332289] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No stroke 57 (50-69) 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | X | X | X | X | | X | Stroke (cerebral infarct) Total Ca (food) |
| Marniemi 2005 ⁴⁸ Turku Finland (60°N) [15955467] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Any 79 (65-99) 48% | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Interview No | Outcome stratified by total Ca intake tertiles | X | X | | | | X | MI Stroke Total Ca (both) |

continued

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Specific CVD Outcomes | | | |
|---|--|---|---|--|--|---------|---------|-------------|--------------------------|--|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | | | | |
| Ross 1997 ^{113A} Shanghai China (31°N) [9236416] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Cases & controls nd (45-64) 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ nd | Outcome stratified by total Ca intake tertiles | | X | X | X | | X | Fatal stroke Total Ca (food) |
| Umesawa 2006 ¹⁰⁴ Japan CC Japan (various) [16339476] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No CVD 56 (40-79) 39 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | X | X | X | X | | X | Cardiac death Stroke death CVD death Total Ca (food) |
| Umesawa 2008 ¹⁰⁶ Japan PHC Japan (various) [18635855] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No CVD 49 (40-59) 48 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Outcome stratified by total Ca intake quintiles | X | X | X | X | | X | CHD Stroke Total Ca (food) |
| van der Vijver 1992 ¹⁰⁵ Dutch civil servants Amsterdam Netherlands (52°) [1544755] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Any 52 (40-65) 51 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | | X | X | | | X | Cardiac death CVD death Total Ca (food) |
| Weng 2008 ¹⁰⁸ CVD— FACTS Taiwan (22°-25°) [18988909] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No stroke, cancer 57 (≥40) 44 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quartiles (top 2 quartiles combined) | | X | X | X | | X | Ischemic stroke Total Ca (both) |

^A Nested case-control study

^B This table is ordered alphabetically by study author

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

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

continued

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

continued

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

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

* Statistically significant ($P < 0.05$)

^A Case-control study from prospective, longitudinal cohort.

Figure 11. Cardiovascular outcomes risk stratified by calcium intake

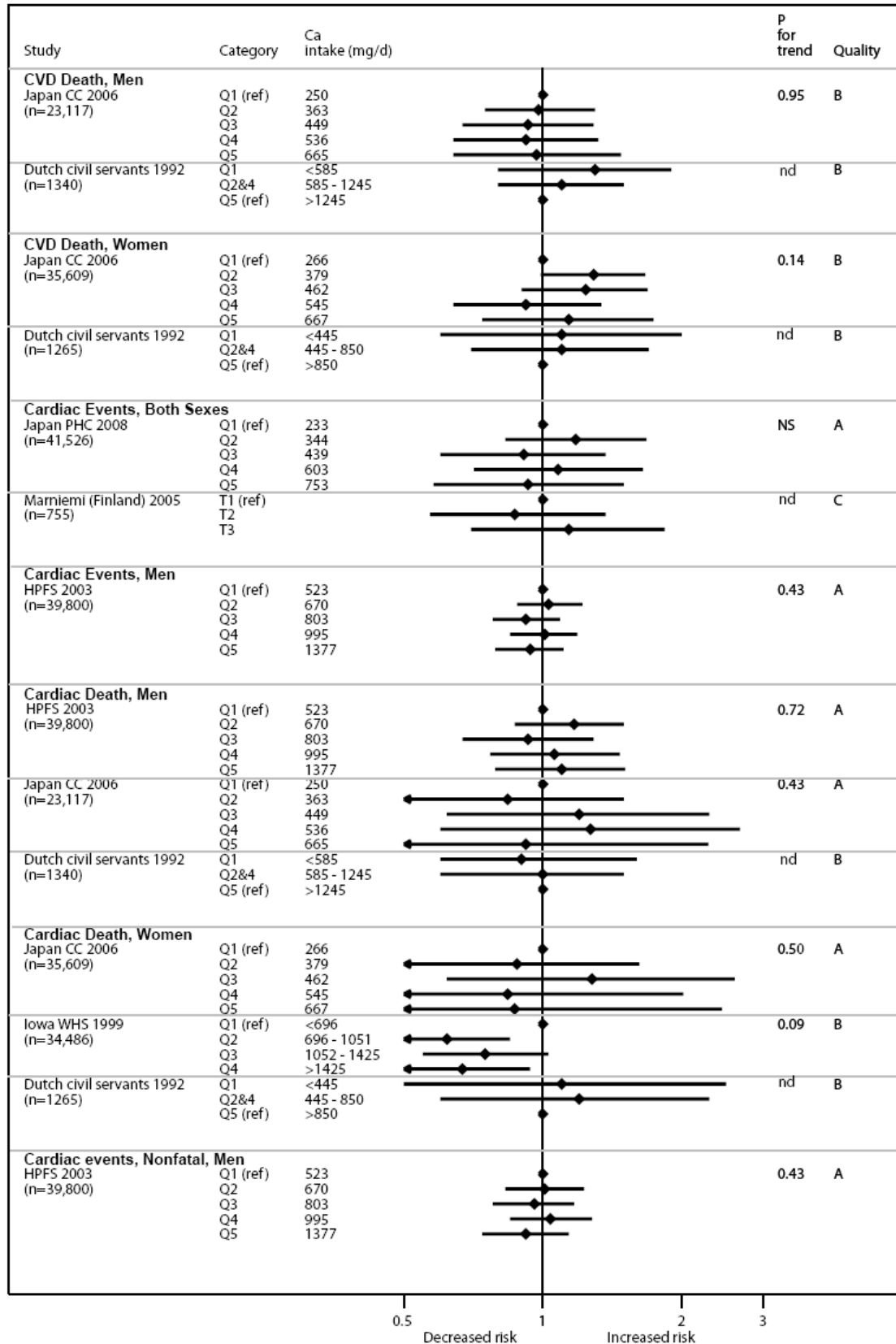
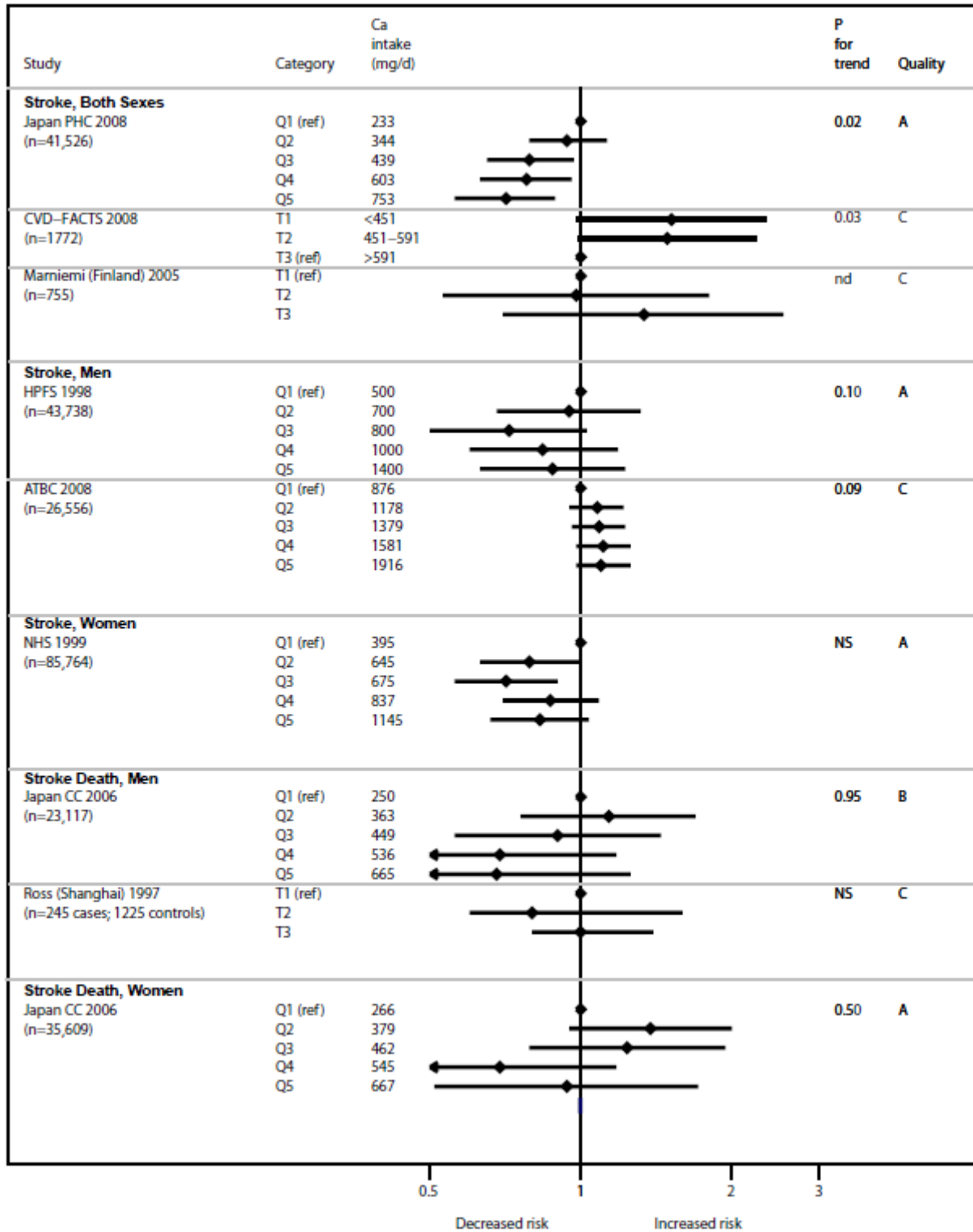


Figure 12. Stroke risk stratified by calcium intake



Calcium and Body Weight

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

Synopsis.

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

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

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

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

The three systematic reviews explicitly or implicitly used generally different eligibility criteria, resulting in large overlaps in the trials included among the reports.¹¹⁴⁻¹¹⁶ Overall, the systematic reviews included 42 trials. All systematic reviews separately analyzed calcium supplementation and dairy product intake. The largest, most recent systematic review¹¹⁴ included trials up to 2007, separated isocaloric from energy-restricted trials, but did not perform meta-analysis. The next largest systematic review¹¹⁵ included trials through 2004. The last systematic review,¹¹⁶ through 2001, also did not perform meta-analyses. All the dairy product trials in this review were also included in the most recent systematic review and are thus not discussed further here. Seven more recent calcium supplementation trials not included in any of the systematic reviews were found.¹¹⁷⁻¹²³

Isocaloric trials.

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

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

Findings per calcium intake level.

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

Findings per age and sex

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

Energy-restricted diets.

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

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

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

Findings per calcium intake level.

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

Findings per age and sex.

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

Combined isocaloric and energy-restricted diets.

Two of the systematic reviews did not separately analyze studies based on background diet (regarding weight). The systematic review by Trowman et al. (2006)¹¹⁵ performed meta-analyses of 13 trials, separately for calcium supplement and dairy product trials. This systematic review found a significant effect of calcium supplements (weighted mean difference = -1.79 [95 percent CI -3.04, -0.55]) suggesting greater weight loss (or smaller weight gain) in adults taking calcium supplements. However, the investigators noted that the difference in effect of calcium supplement trials may be due to significant differences (in aggregate) in the baseline weights of the two arms. Across studies, the calcium supplement group participants had significantly lower body weights at baseline. The meta-analysis of dairy trials found no significant effect of dairy products on body weight. The systematic review by Barr et al. (2003)¹¹⁶ reviewed both calcium supplement and dairy trials; however, the dairy trials were all included in the later systematic review by Lanou et al. (2008)¹¹⁴ and are thus not repeated here. Among the eight trials of calcium supplementation, all but one found no significant effect on body weight. Between the two systematic reviews, over two-thirds of the trials were conducted in post- or perimenopausal women; the mean age of participants (among trials with data reported in the systematic reviews) ranged from 36 to 72 years. Only four of the trials were conducted in men. The range of calcium supplement doses was 700 to 1600 mg/day, with most studies using 1000 mg. The range of calcium intake among the dairy trials was 610 to 2400 mg/day. In the Trowman et al. (2006) systematic review,¹¹⁵ the range of followup durations of the trials was 12 weeks to 3 years. The Barr et al. (2003) systematic review¹¹⁶ included longer duration trials, ranging from 6 months to 4 years.

Findings per calcium intake level.

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

Findings per age and sex.

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

Findings by life stage.

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

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

Table 51. Systematic reviews of calcium supplementation and weight

| | | | |
|--|--|---|-----------|
| Author Year [PMID] | Lanou 2008 ¹¹⁴ [18454813] | | |
| Design (Search Years) | Randomized controlled trials (1966-2007) | | |
| Population | All, generally healthy (adults and children, only studies of adults included here) | | |
| Intervention and Comparator | Calcium supplements or dairy intake versus no supplement or low calcium intake | | |
| Results | 29 trials ^a No energy restriction Calcium supplement: 8/9 trials no significant effect. 1 found significantly more weight loss on calcium supplement. Dairy supplementation: 8/10 trials no significant effect. 2 found significantly more weight gain among those on dairy Energy restriction Calcium supplement: 4/5 trials no significant effect. 1 found significantly more weight loss with calcium. Dairy supplementation: 3/6 trials significantly more weight loss on high calcium intake All 4 trials with significant differences were by same study investigators | | |
| Comments | | | |
| AMSTAR | | | |
| A priori design? | Yes | Study quality assessment performed? | No |
| Two independent reviewers? | nd | Study quality appropriately used in analysis? | NA |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | None |
| All publication types and languages included? | No | Publication bias assessed? | No |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No |
| Study characteristics provided? | Only published trials. Excluded studies not enumerated or listed. | | |
| Author Year [PMID] | Trowman 2006 ¹¹⁵ [16768823] | | |
| Design (Search Years) | Randomized controlled trials (1800 ^b /2002-2004) | | |
| Population | Nonpregnant, nonlactating, ≥18 y | | |
| Intervention and Comparator | Calcium supplements or dairy intake versus no supplement or low calcium intake | | |
| Results | 13 trials Calcium supplement WMD = -1.79 (-3.04, -0.55) ^c , statistically homogeneous Dairy supplementation WMD = +0.85 (-4.39, +6.08), statistically heterogeneous ANCOVA, adjusting for baseline weight: Calcium Effect = -0.41 (-1.07, +0.25) kg Dairy Effect = +0.23 (-2.88, +3.34) kg | | |
| Comments | Apparent difference in effect of calcium supplement trials may be due to significant differences (in aggregate) in baseline weights of two arms across studies (intervention arm participants were significantly lighter at baseline). | | |
| AMSTAR | | | |
| A priori design? | Yes | Study quality assessment performed? | No |
| Two independent reviewers? | nd | Study quality appropriately used in analysis? | NA |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Debatable |
| All publication types and languages included? | Yes (implied) | Publication bias assessed? | Yes |
| Included and excluded studies listed? | No | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | Excluded studies not enumerated or listed. Used WMD instead of net difference, then needed to perform an ANCOVA to adjust for baseline differences. | |

continued

| | | | |
|--|--|---|------|
| Author Year [PMID] | Barr 2003 ¹¹⁶ [12514301] | | |
| Design (Search Years) | Randomized controlled trials (1966-2001) | | |
| Population | All, generally healthy (adults and children, only studies of adults included here) | | |
| Intervention and Comparator | Calcium supplement or dietary calcium versus no supplement or usual calcium intake (see Comment) | | |
| Results | 8 trials | 7/8 trials found no significant effect | |
| Comments | 6 dairy supplementation trials reviewed. Not included here. These represent a subset of the dairy trials reviewed by Lanou 2008 ¹¹⁴ | | |
| AMSTAR | | | |
| A priori design? | Yes | Study quality assessment performed? | No |
| Two independent reviewers? | nd | Study quality appropriately used in analysis? | NA |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | None |
| All publication types and languages included? | No | Publication bias assessed? | No |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No |
| Study characteristics provided? | Yes | Studies published in English only. Excluded studies not enumerated or listed. | |

WMD, weighted mean difference

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

^B Cochrane Library Database of Controlled Trials

^C Numbers in parentheses are 95% confidence intervals

Table 52. Calcium and weight: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments | |
|---|---|--|-------------------------------------|--|--|---|
| Yamamoto 1995 ¹¹⁷ TOHP US (various) [7795837] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | <p>Healthy</p> <p>43 (30-54)</p> <p>69</p> | Ca 970 mg/d | Ca carbonate vs placebo | Eligibility for randomization required consumption of at least two-thirds of 6 wks of supplement placebo dosing. During the study, pill counts averaged 95% (with three-fourths taking at least 95% of their supplements). | |
| van Beresteyn 1986 ¹¹⁸ Netherlands (52°N) [3788835] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | <p>Healthy</p> <p>21 (20-23)</p> <p>0</p> | nd | Ca carbonate vs placebo | nd | |
| Cifuentes 2004 ¹¹⁹ New Brunswick, NJ (40°N) [15213038] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | <p>Overweight, post-menopause</p> <p>61 (52-75)</p> <p>0</p> | nd | Ca supplement vs placebo | nd Factorial design with weight loss and maintenance diets | |
| Ghadirian 1995 ¹²⁰ Montreal, Canada (46°N) [7493659] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | <p>Healthy, post-menopause</p> <p>~80 (~≥50)</p> <p>0</p> | Ca 776 mg/d | Dairy vs dairy free intake | Non-compliant and those who provided incomplete data were excluded. | |
| Aloia 1995 ¹²¹ Mineola, NY (41°N) [7892882] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | <p>Healthy, post-menopause</p> <p>53 (0.6)</p> <p>0</p> | nd | Ca supplement vs placebo (Vit D in both groups) | nd | |
| Thomsen 1987 ¹²² Copenhagen, Denmark (55°N) [3307307] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | <p>Healthy, post-menopause</p> <p>nd</p> <p>0</p> | nd | Combination Ca lactate-gluconate & Ca carbonate vs placebo | nd | |
| Bortolotti 2008 ¹²⁴ Lausanne, Switzerland (47°N) [18842771] | <ul style="list-style-type: none"> • Health status • Mean age (SE), y • Male (%) | <p>Healthy</p> <p>22 (1.2)</p> <p>30</p> | Ca 586 (137 SE) mg/d, all <800 mg/d | Ca phosphate vs placebo | Measured but not reported | Crossover study (5 wk with 10 wk washout), 1° outcomes were metabolic |
| Kabrnova-Hlavata 2008 ¹²³ Lausanne, Czech Rep (50°N) [17552880] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) • Male (%) | <p>Overweight, healthy</p> <p>49 (12)</p> <p>0</p> <p>0</p> | nd | Ca carbonate vs "lactoval" vs placebo | nd (a dietitian checked that subjects took tablets) | Energy restriction |

Table 53. Calcium and weight: Results of RCTs

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

continued

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

^A Subgroup data available for black and white men and women (4 groups). No substantive differences among groups. All statistically nonsignificant.

^B Estimated from reported data

^C Adjusted for multiple factors, including baseline weight.

^D No data on calcium type

^E Crossover study

^F Adjusted for multiple factors, including baseline weight

Calcium and Cancer

Cancer from all cause and total cancer mortality.

Synopsis.

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

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

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

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

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

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

Findings by age, sex and/or ethnicity.

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

Findings by life stage.

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

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|---|---|--|------------|----------|
| Lappe 2007 ⁵² Nebraska, US 41° N [17556697] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Mentally and physically fit 67 (7.3) 0 | 25(OH)D: 71.8 nmol/L Vit D ₃ 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo | | |

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|---|---|------------------------|---|---|---|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Cohort | | | | | | | | | | | | |
| Park 2009 ¹²⁵ NIH-AARP US 38° N [19237724] | <ul style="list-style-type: none"> • Health status • Mean age (range/), y • Male (%) | No cancer 50-71 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ (NCI-DHQ) USDA Nutrient Database y | Total cancer risk stratified by quintile of total calcium intake | X | X | X | X | | X | Total calcium intake from diet and supplement |
| Slob 1993 ¹²⁶ Amsterdam 52° N [8478144] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | nd 53 (40-65) 51 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ no | Cancer mortality stratified by dietary calcium intake quintiles (from foods only) | X | X | | | | | |

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

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

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

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

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

Prostate cancer.

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

Synopsis.

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

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

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

19-50 years.

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

51-70 years.

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

Findings by life stage.

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

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

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

continued

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

continued

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

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

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

Continued

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

Continued

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

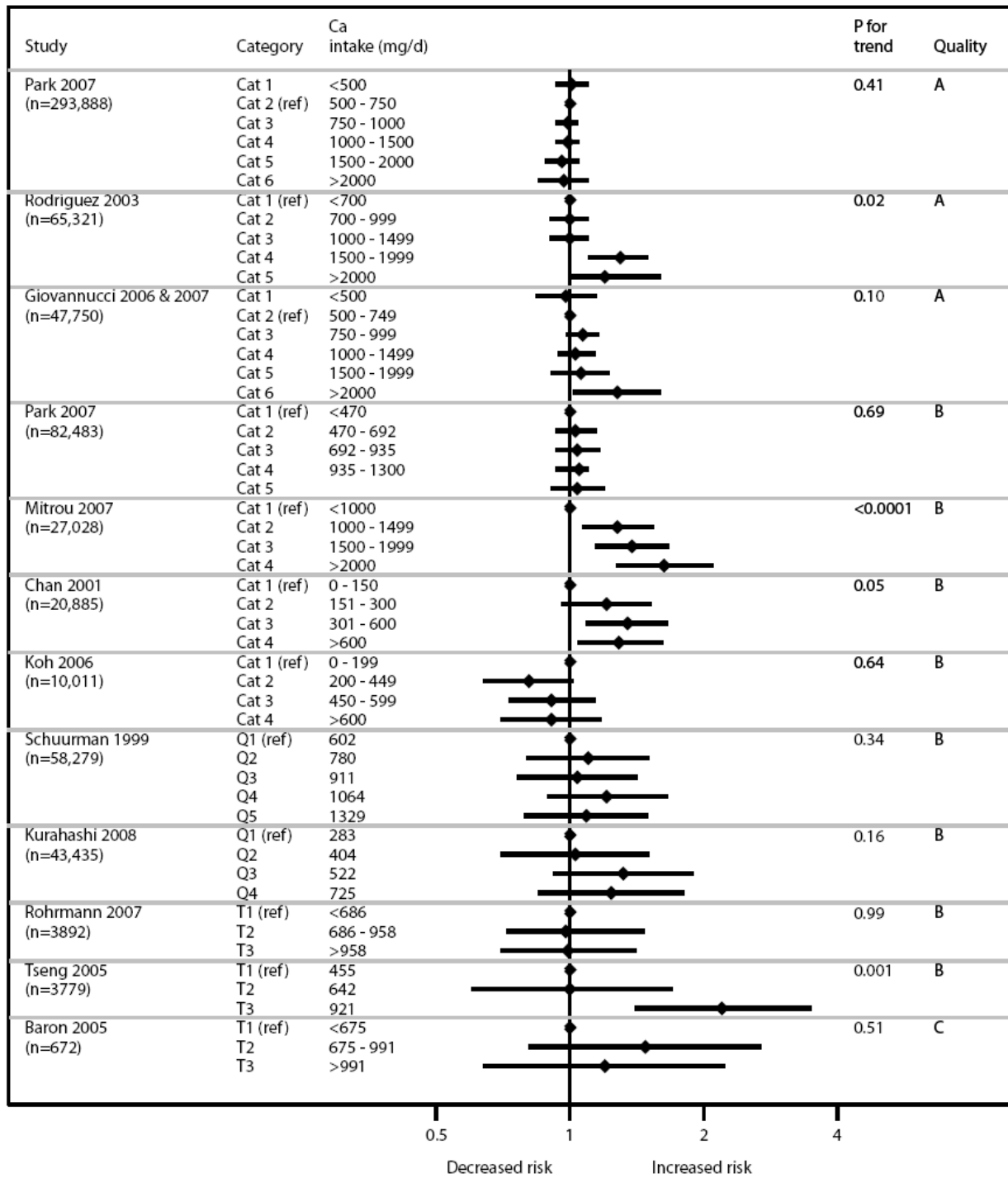
* Statistically significant (P<0.05)

^A Dietary calcium

^B median of tertile, quartile or quintile

^C Adjusted hazard ratio

Figure 13. Prostate cancer risk stratified by calcium intake



Colorectal cancer.

Synopsis.

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

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

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

Nineteen cohort studies in 20 publications^{125,140-158} and one nested case-control study¹⁵⁹ evaluated the association between calcium intake and colorectal, colon, or rectal cancer. Sample sizes ranged from 1954 to 492,810. Half of the studies were conducted in the US (latitude ranged from 21° N to 54° N),^{125,140,142,144,145,147,150-152,154,155,158} one study was conducted in China (latitude 31° N),¹⁴⁹ and the rest were conducted in Europe including France (latitude 46° N),¹⁴¹ the Netherlands (latitude 52° N),¹⁵⁹ the United Kingdom (latitude ranged between 54° N and 55° N),¹⁵⁶ and Scandinavia (latitude ranged between 59° N and 69° N).^{143,146,148,153,157} For colorectal cancer, the incidence ranged from 0.003 to 0.025 for cohorts, while in the nested case-control study, the colorectal cancer incidence was 0.142; for colon cancer, the incidence ranged from 0.003 to 0.024; and for rectal cancer, the incidence ranged from 0.003 to 0.004. The participants' mean age ranged from 7.6 to 61.9 years. Average followup ranged from 1.4 to 19.6 years. Only one study reported that exposure assessors were blinded to outcome.¹⁵⁴ No studies mentioned that outcome assessors were blinded to exposure. None of the studies reported power calculations. The majority of the studies evaluated the potential effect of various factors besides calcium on colorectal cancer. All performed analyses adjusted at least for age. Except for four studies^{151,156-158} that used dietary history, all other studies used a food frequency questionnaire to assess dietary intake. More than half of the studies did not confirm all or part of cancer cases with pathology reports. Six studies^{125,140-143,159} were rated B, and 15 publications¹⁴⁴⁻¹⁵⁸ were rated C for methodological quality.

Findings by age, sex and/or ethnicity.

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

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

Out of four cohort studies^{145,148,151,153} that analyzed men, one¹⁴⁵ found an inverse association between total calcium intake and colon cancer in a subgroup analysis. Out of four cohort studies^{146,147,150,153} that analyzed women, none found an association between total calcium intake and colon cancer. For rectal cancer, one¹⁴⁸ of two^{145,148} studies that analyzed men and one¹⁵² of three^{146,147,152} studies that analyzed women found an inverse association between total calcium intake and rectal cancer.^{148,152}

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

Findings by life stage.

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

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

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

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

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

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

| Author, Year Trial/Cohort Name Country (Latitude) [PubMed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|--|---|---|---|--|---------|---------|---------|-------------|----------|---|---|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | Life styles | | | |
| Cohort | | | | | | | | | | | | |
| Park, 2009 ¹²⁵ NIH-AARP Diet & Health (various) US [19237724] | <ul style="list-style-type: none"> • Health status • Mean age range, yr • Male (%) | Generally healthy men and women 50-71 60 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Semi-quantitative FFQ (NCI-DHQ) y | CRC across 5 categories of total calcium intake | X | X | X | X | | X | White Male ~92%; Female ~89%; Total Ca (both) |
| Wu, 2002 ¹⁴⁰ HPFS NHS (various) US [11904316] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | HPFS: generally healthy male health professionals NHS: generally healthy female nurses HPFS: 54.4 NHS: 46.6 HPFS: 100 NHS: 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | HPFS: 131-item semi-quantitative FFQ (by Willet) NHS: 61-item semi-quantitative FFQ (by Willet) y | For HPFS, NHS separately: CRC across 7 categories of cumulative average calcium intake | X | X | X | X | | X | Total Ca (both) |
| Kesse, 2005 ¹⁴¹ Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women 52.7 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ y | CRC across total calcium intake quartiles | X | X | X | | | X | Total Ca (food) |
| Lin, 2005 ¹⁴² WHS US (various) [15800268] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 131-item FFQ y | CRC across total calcium intake quintiles | X | X | X | X | | X | Total Ca (both) |

continued

| Author, Year Trial/Cohort Name Country (Latitude) [PubMed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|---|--|---|---|--|--|---------|---------|---------|-------------|----------|---|--------------------------|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | Life styles | | | |
| Pietinen, 1999 ¹⁴³ ATBC Finland (~64°N) [10530608] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men; smokers Median, cases: 60.1; non cases: 57.1 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 276-item FFQ y | CRC across total calcium intake quartiles | X | X | X | | | X | Total Ca (food) |
| Park, 2007 ¹⁴⁴ The Multiethnic Cohort Study US (various) [17215380] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women nd 45 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ y | CRC per gender across total calcium intake quintiles | X | X | X | X | | X | Total Ca (both) |
| McCullough, 2003 ¹⁴⁵ CPS II US (various) [12708719] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women nd 48 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 68-item semi-quantitative FFQ (modification of the brief Health Habits and History Questionnaire (HHHQ) by Block) y | CRC across total calcium intake quintiles Subgroup analyses per gender For men, subgroup analyses per site (colon, rectal) | X | X | X | X | | X | Total Ca (both) |
| Shin, 2006 ¹⁴⁹ Shanghai Women's Health Study China (31°N) [17019716] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women Cases: 59 (8.5); non-cases: 52 (9.1) 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 77-item FFQ used in Shanghai Women's Health Study y | CRC across total calcium intake quintiles Subgroup analyses per site (colon, rectal) | X | X | | X | | X | Chinese; Total Ca (food) |

continued

| Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Comments | | |
|--|--|--|---|---|---|---------|---------|---------|----------|-------------|--|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | | Life styles | |
| Terry, 2002 ¹⁴⁶ Swedish Mammography Screening Cohort Sweden (59°N) [12467133] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women and | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Self-administered 67-item FFQ y | CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal) Subgroup analyses per age (< 55 vs. ≥ 55 years old) and site (colon, rectal) | X | X | X | | X | Total Ca (food) |
| Gaard, 1996 ¹⁵³ and Norway (60°-69°N) [9061275] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women 43 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | semi-quantitative FFQ (Oslo University) y | Colon cancer per gender across total calcium intake quartiles | | X | X | | X | Total Ca (food) |
| Flood, 2005 ¹⁴⁷ The Breast Cancer Detection Demonstration Project (BCDDP) US (various) [15668485] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women 61.9 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 62-item semi-quantitative FFQ (by Block) y | CRC cancer across total calcium intake quintiles Subgroup analyses per site (colon, rectal) | X | X | X | X | X | Total Ca (both) |
| Larsson, 2006 ¹⁴⁸ The Cohort of Swedish Men Sweden (59°N) [16522915] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men 60.3 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 96-item semi-quantitative FFQ y | CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal) | X | X | X | X | X | Total Ca (both) |
| Bostick, 1993 ¹⁵⁰ Iowa Women's Health Study US (40°N) [8333412] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy post-menopausal women 61.5 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 127-item semi-quantitative FFQ (by Willet) y | Colon cancer across total calcium intake quintiles | X | X | X | | | Same cohort as Zheng 1998; Total Ca (both) |

continued

| Author, Year Trial/Cohort Name Country (Latitude) [PubMed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Comments | | | |
|--|--|--|---|---|---|---------|---------|---------|----------|-------------|---|--|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | | Life styles | | |
| Zheng, 1998 ¹⁵² Iowa Women's Health Study US (40°N) [9521437] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy post-menopausal women 61.5 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 127-item semi-quantitative FFQ (by Willet) y | Rectal cancer across total calcium intake tertiles | X | X | X | X | | X | Same cohort as Bostick 1993; Total Ca (both) |
| Kato, 1997 ¹⁵⁵ New York University Women's Health Study US (various) [9343837] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy women nd 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 70-item semi-quantitative FFQ (slightly modified from Block's) y | CRC across total calcium intake quartiles | X | X | | | | | Total Ca (food) |
| Wu, 1987 ¹⁵⁴ US (21°N) [3620314] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women nd 33 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 56-item FFQ n | CRC per gender across total calcium intake tertiles | | X | | | | | Total Ca (dairy) |
| Jarvinen, 2001 ¹⁵⁷ nd Finland (64°N) [11641750] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women 39.1 nd | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Diet history y | CRC across total calcium intake quartiles Subgroup analyses per site (colon, rectal) | X | X | X | | | X | Total Ca (food) |
| Stemmerman, 1990 ¹⁵¹ Japan Hawaii Cancer Study US (21°N) [2311461] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men nd 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 24-hour diet recall interview y | Colon cancer across total calcium intake tertiles | | X | | | | | Japanese; Total Ca (food) |

continued

| Author, Year Trial/Cohort Name Country (Latitude) [PubMed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | Comments | | |
|--|--|---|---|--|--|---------|---------|---------|----------|-------------|-----------------|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | | Life styles | |
| van der Pols, 2007 ¹⁵⁶ The Boyd Orr Cohort UK (54°-55°N) [8333412] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy children 7.6 49.5 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 7-day household inventory method n | CRC between lowest and highest total calcium intake groups | X | X | X | | X | Total Ca (food) |
| Garland, 1985 ¹⁵⁸ Western Electric Health Study US (41°N) [2857364] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men 48.7 (4.4) 100 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 28-day diet histories n | CRC across total calcium intake quartiles | X | X | X | | X | Total Ca (food) |
| Nested case-control | | | | | | | | | | | |
| Kampman, 1994 ¹⁵⁹ The Netherlands Cohort Study Netherlands (52°N) [8205538] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), yr • Male (%) | Generally healthy men and women nd nd | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 150-item semi-quantitative FFQ y | CRC across total calcium intake quintiles | X | X | | X | X | Total Ca (food) |

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

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

continued

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

continued

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

continued

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

continued

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

continued

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

continued

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

continued

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

continued

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

continued

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

continued

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

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

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

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

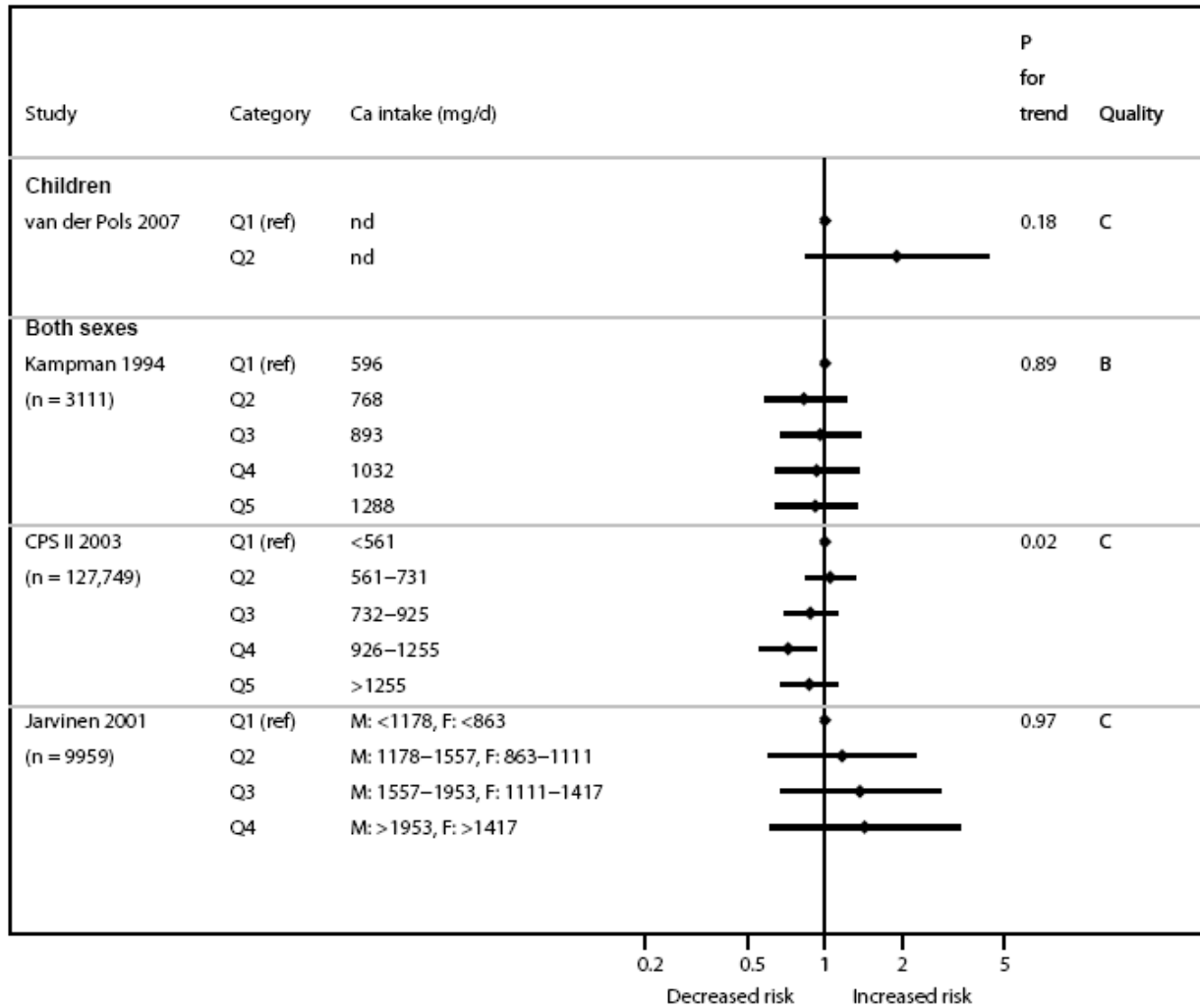


Figure 15 Colorectal cancer risk in men stratified by calcium intake

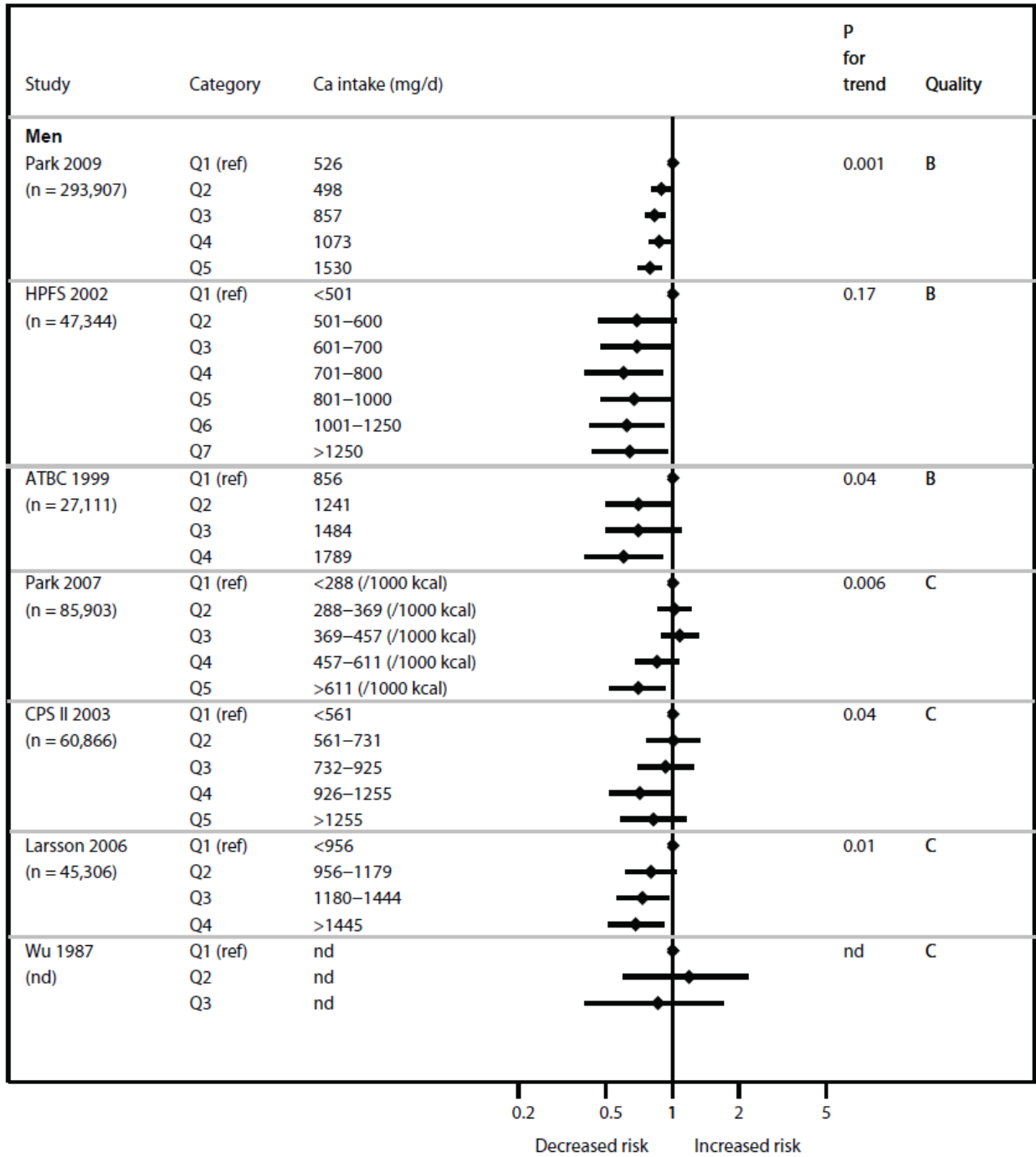


Figure 16 Colorectal cancer risk in women stratified by calcium intake

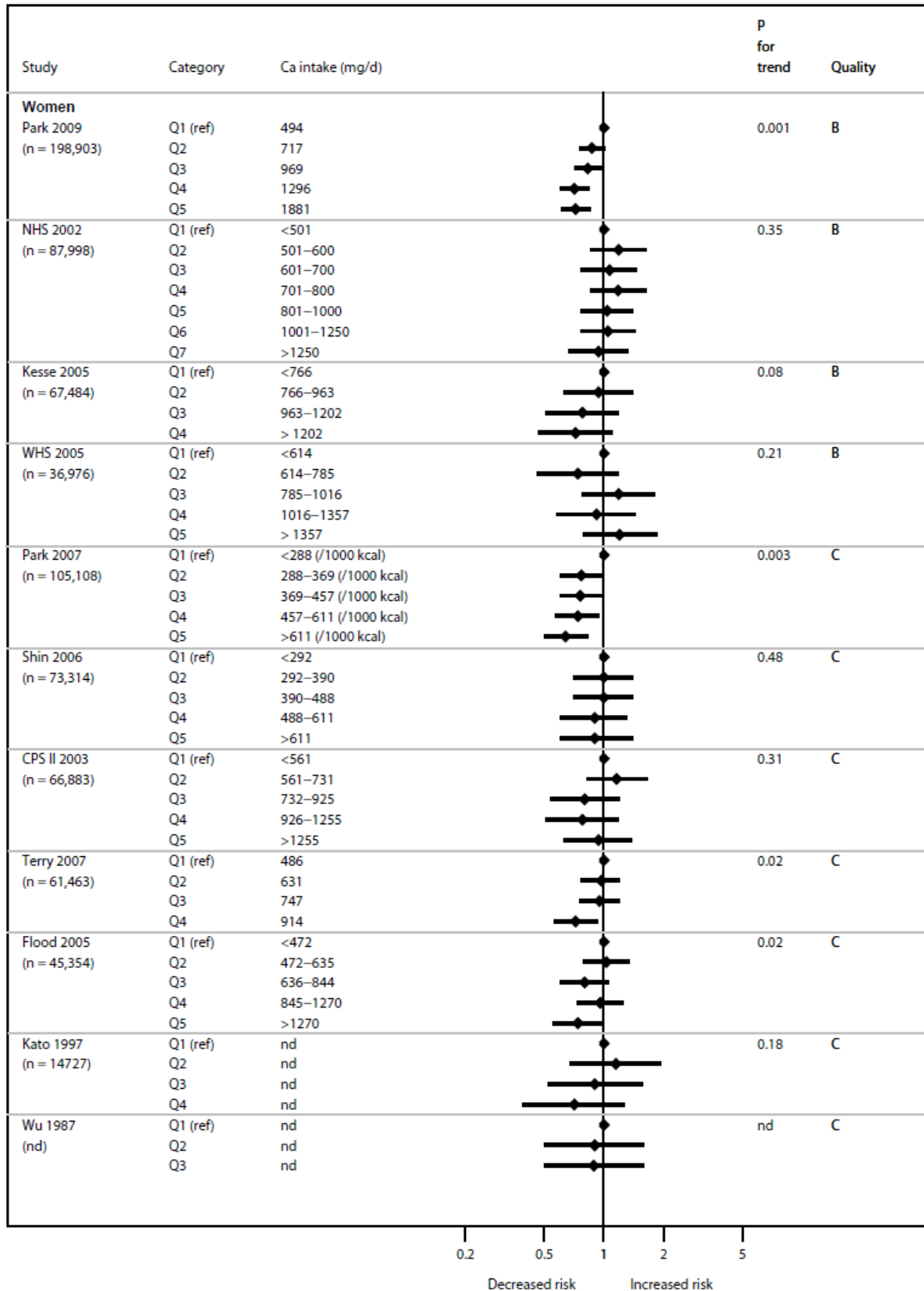


Figure 17 Colon cancer risk stratified by calcium intake

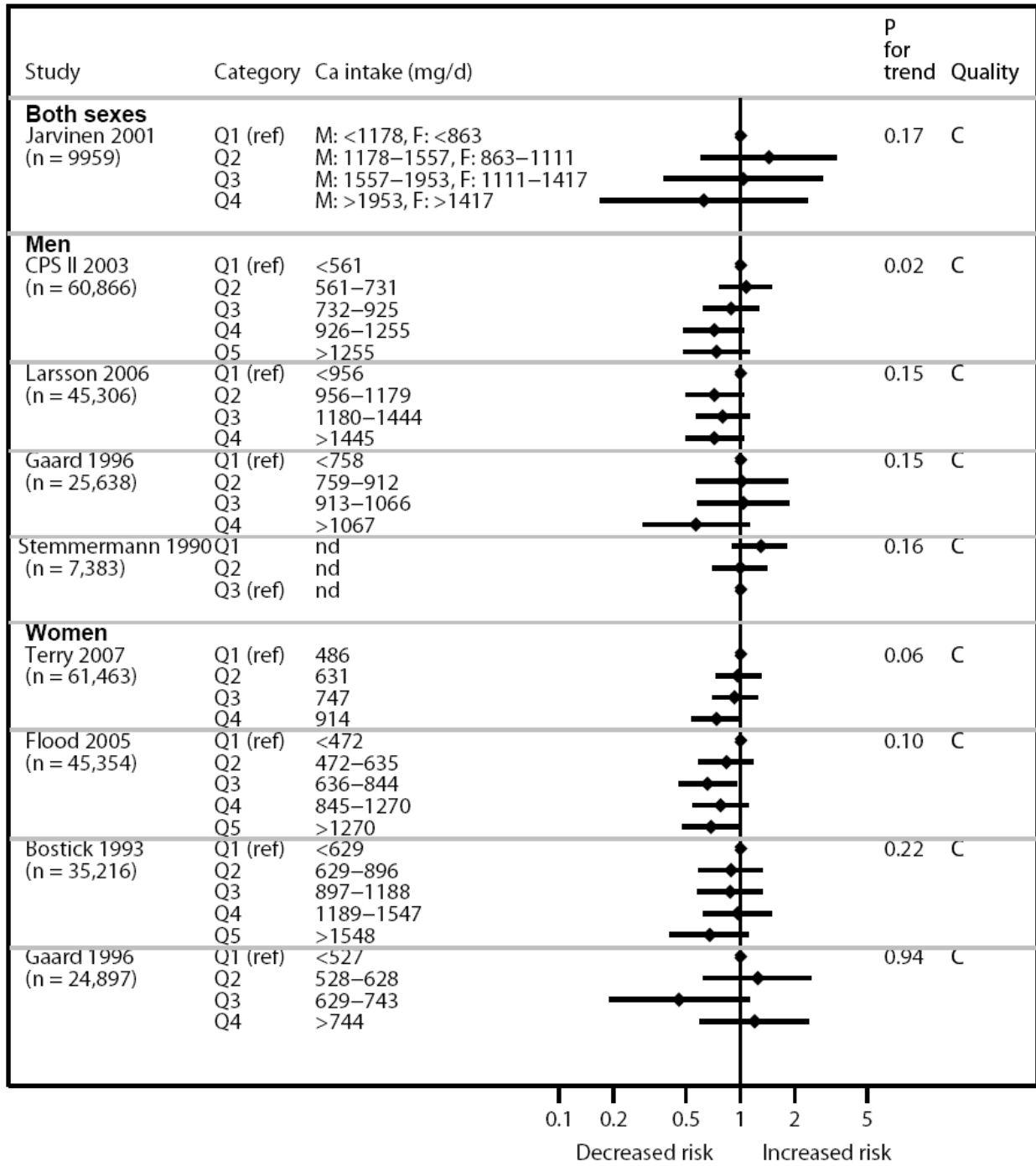
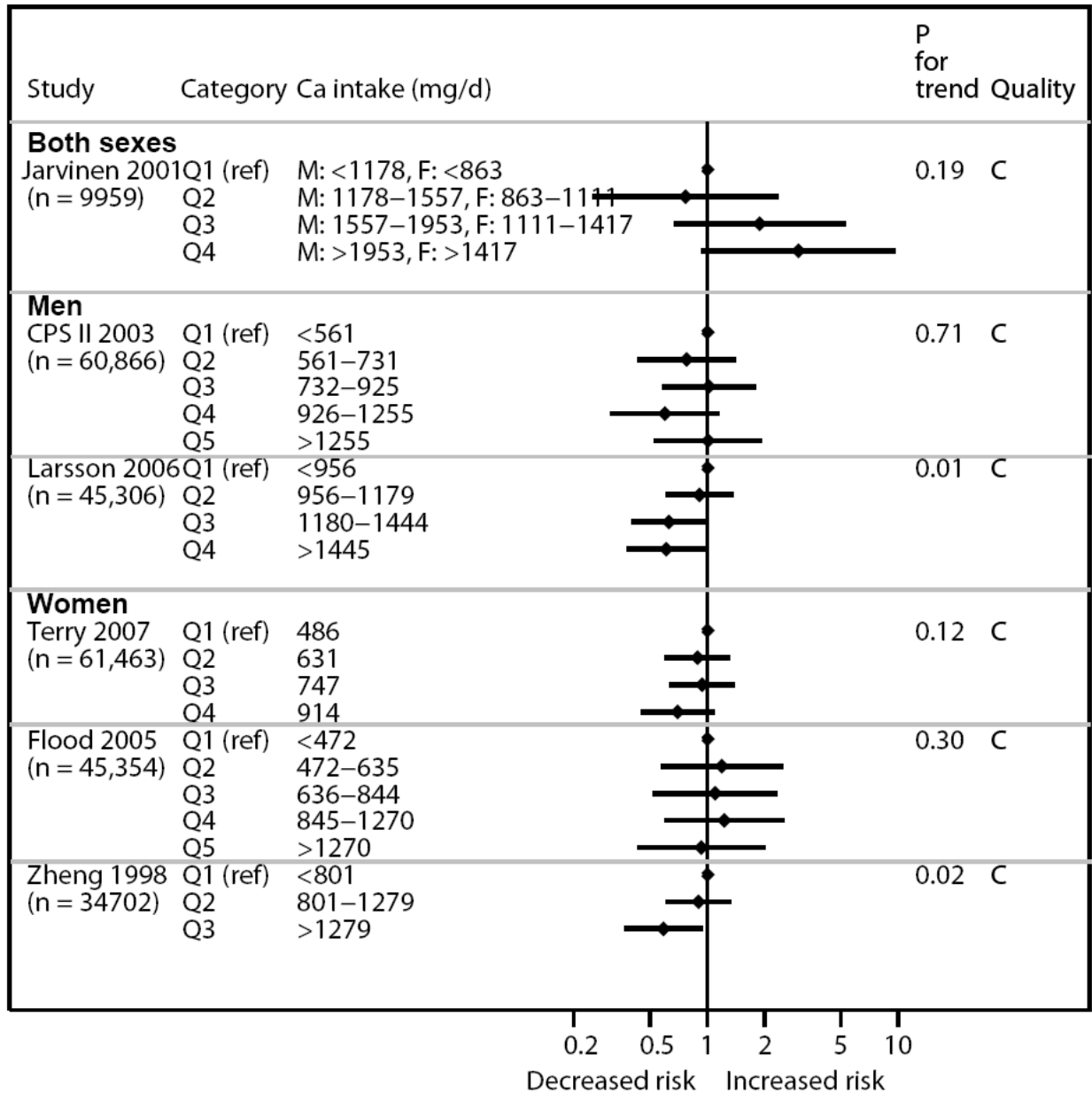


Figure 18. Rectal cancer risk stratified by calcium intake



Colorectal adenoma.

Synopsis.

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

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

One systematic review included two RCTs that recruited high risk population for colorectal adenoma due to previous adenomatous polyps.¹³⁹ A total of 1346 participants were analyzed for the effect of calcium supplementation (1200 to 2000 mg elemental calcium daily). The odds ratio of colorectal adenoma recurrence was 0.74 (95 percent CI 0.58, 0.95; P=0.02), comparing calcium supplementation to the placebo. A B quality post hoc followup analysis¹⁶¹ of one of the two RCTs that were included in the meta-analysis examined the long-term effect of calcium supplementation to prevent colorectal adenoma recurrence. The trial recruited participants with previous colorectal adenoma, and compared the preventative efficacy of calcium supplementation (1200 mg/d) to placebo. Adenoma recurrence at 4 years was the original primary outcome. During the followup period after the trial treatment, about 50 percent of participants in both groups took some calcium supplements. In 347 participants who underwent colonoscopy during the first 5 years after the intervention period, the relative risk of adenoma recurrence was 0.63 (95 percent CI 0.46, 0.87; P=0.005) comparing calcium supplementation to placebo, whereas no difference was found in 424 participants who underwent colonoscopy in the subsequent 5 to 10 years after the trial treatment.

A nonrandomized comparative study¹⁶² presented the percentage of adenoma recurrence in a group of men and women who underwent polypectomy, and received calcium supplementation (2000 mg/d) as chemoprevention. The same study also presented the percentage of adenoma recurrence in a group of men and women who underwent polypectomy but were not supplemented with calcium. The intervention group included 175 participants while the nonsupplemented group included nine patients. The two groups were followed for an average of 3.1 years. The trial was rated C for methodological quality. In this study,¹⁶² the percentage of participants with adenoma recurrence was lower in the intervention group compared to the nonsupplemented participants (13 percent versus 55 percent); however, no further statistical analysis was provided.

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

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

Findings by age and sex.

One cohort study¹⁶⁵ that analyzed men and women (aged 40-80 y) with a history of colorectal adenoma found an inverse association between total calcium intake and colorectal adenoma recurrence after an average of 3.1 years of followup (RR 0.62, highest [>1279 mg/d] compared with lowest intake [<778 mg/d]; P for trend = 0.005). The study did not test statistically whether the strength of the association differed between men and women. Another study of both men and women with previous adenomatous polyps found no significant association between total calcium intake and colorectal adenoma recurrence.

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

Findings by life stage.

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

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

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

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

| Author, Year Trial/Cohort Name Country (Latitude) [Pubmed ID] | Population | Vit D & Ca Background Diets | Interventions | Compliance | Comments |
|--|---|--|--------------------------------------|------------------------------|--|
| RCTs | | | | | |
| Grau, 2007 ¹⁶¹ Calcium Polyp Prevention Study ^A US (34°-44°N) [17227996] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy men and women with a recent colorectal adenoma 60.6 71.7 | Calcium, mean: 876 mg/d ^B | Elemental calcium, 1200 mg/d | nd Duplicated with Wallace; results during the observational post-intervention phase (5-10 years) |
| Nonrandomized comparative study | | | | | |
| Duris, 1996 ¹⁶² nd Slovakia (48°N) [8682453] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy men and women; history of adenomatous polyps after polypectomy 54.7 62 | nd | Calcium carbonicum (2 g/d) | No statistical comparison between groups |

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

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

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

| Author, Year Trial/Cohort Name Country (Latitude) [PubMed ID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|---|--|---|---|--|---------|---------|---------|-------------|----------|---|-----------------|
| | | | | Nutrients | Demographic | Anthrop | Medical | Seasons | Life styles | | | |
| Cohort | | | | | | | | | | | | |
| Oh, 2007 ¹⁶³ The Nurses Health Study US (38°N) [17379616] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy women 30-55 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 61-item semi-quantitative FFQ (by Willet) y | Colorectal adenoma across total calcium intake quintiles | x | x | x | x | | x | Total Ca (both) |
| Kesse, 2005 ¹⁴¹ Etude Epidémiologique auprès de femmes de l'Education Nationale France (46°N) [15880532] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy women 52.7 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ y | Colorectal adenomas across total calcium intake quartiles | x | x | x | | | x | Total Ca (both) |
| Hartman, 2005 ¹⁶⁴ The Polyp Prevention Trial US (38° N) [15671222] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy men and women; history of at least one colorectal adenoma; 90% Caucasian 61.1 (9.9) 64 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ y | Adenoma recurrence across total calcium intake quintiles | x | x | x | x | | | Total Ca (both) |
| Martinez, 2002 ¹⁶⁵ Wheat Bran Fiber (WBF) trial US (33°N) [12020102] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Generally healthy men and women; history of colorectal adenoma(s) nd 57.1 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 113-item Arizona Food Frequency Questionnaire (AFFQ) y | Adenoma recurrence across total calcium intake quintiles Subgroup analyses per gender | x | x | | x | | | Total Ca (food) |

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

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

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

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

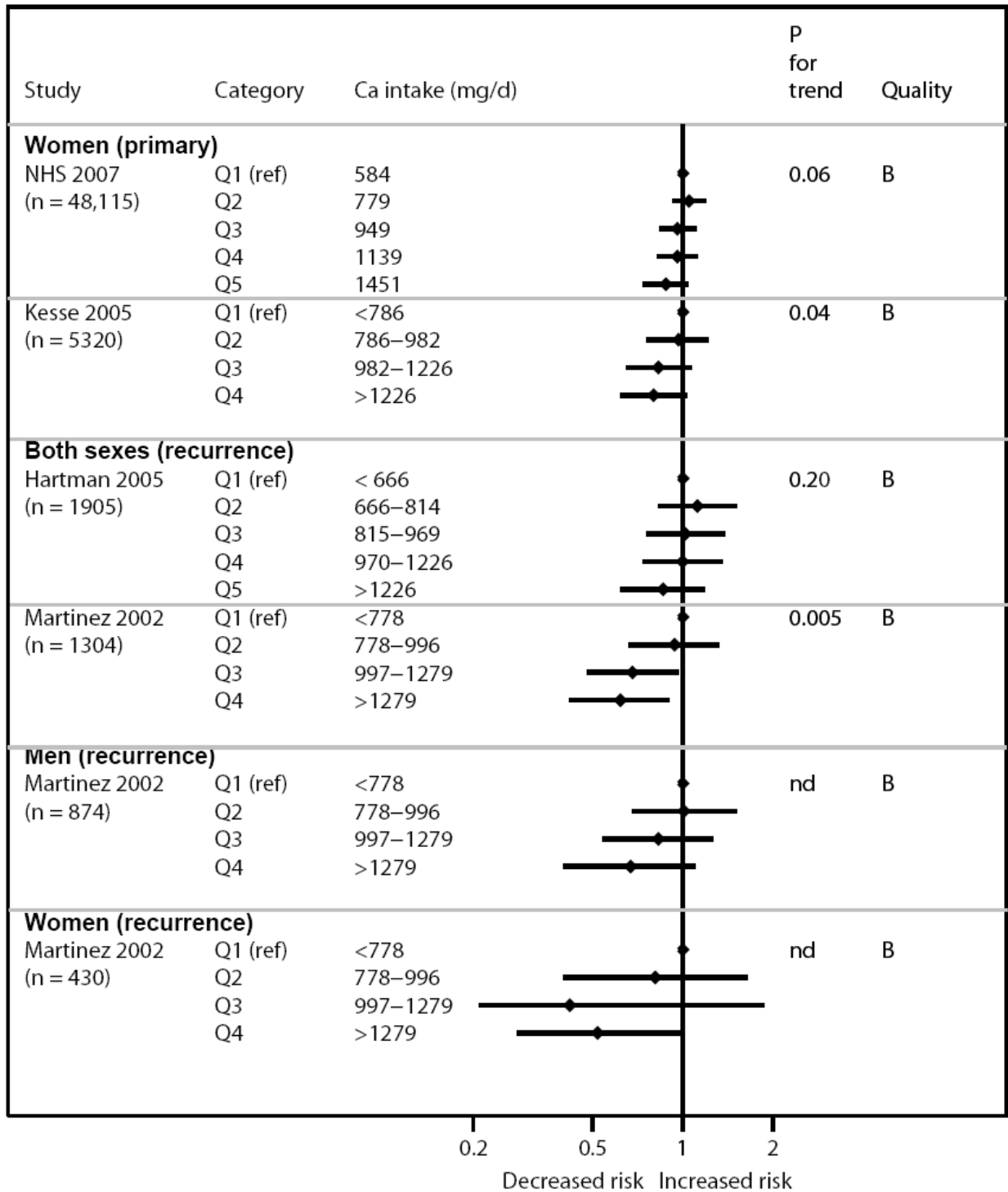
Table 68. Calcium and colorectal adenoma: Results of cohort studies

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

continued

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

Figure 19. Colorectal adenomatous polyp risk stratified by calcium intake



Breast cancer incidence.

Synopsis.

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

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

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

Findings by age and sex.

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

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|---|--------------------------------|---|--|--|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Cohort | | | | | | | | | | | | |
| Park 2009 NIH-AARP US 38° N [19237724] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer 50-71 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ (NCI-DHQ) USDA Nutrient Database y | Quintile 1 vs. Quintile 2, 3, 4, 5 | x | x | x | x | | x | Total calcium intake from diet and supplement |
| Shin 2002 ¹⁶⁹ NHS US 38° N [12208895] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer 47 (ND) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 61 item FFQ USDA Nutrient Database y | 500 mg vs. 500-600, 600-700, 700-800, 800-1000, 1000-1250, >1250 | x | x | x | x | x | x | Total calcium intake from diet and supplement |
| McCullough 2005 ¹⁶⁸ CPS II Nutrition Cohort US 38° N [16365007] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer 63 (ND) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Modified FFQ of Block et al. y | 500 mg vs. 500-750, 750-1000, 1000-1250, 1250-1500, 1500-1750, >1750 | x | x | x | x | x | x | Total calcium intake from diet and supplement |
| Larsson 2009 ¹⁷⁰ Swedish Mammography Cohort Sweden 62° N [19056569] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer 53.7 (9.7) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Swedish National Food Administration Database y | <727 vs. 727-862, 863-980, 980-1125, >1125 | x | x | x | | x | x | Total calcium intake from diet and supplement |
| Lin J 2007 ¹⁶⁷ WHS US 38° N [17533208] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer or CVD 55 (55-56) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Willett method USDA Nutrient Database y | Quintile 1 vs. Quintile 2, 3, 4, 5 | x | x | x | | x | x | Total calcium intake from diet and supplement |

continued

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|---|--------------------------|---|---------------------------------------|---------------------------------|---------|---------|-------------|-----------|----------|---|------------------------|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Kesse-Guyot 2007 ¹⁶⁶ SU.VI.MAX France 46° N [17536191] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y | No cancer 51 (6.3) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | Computerized questionnaires ND | Quintile 1 vs. Quintile 2, 3, 4 | x | x | x | | x | x | Dietary calcium intake |

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

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

continued

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

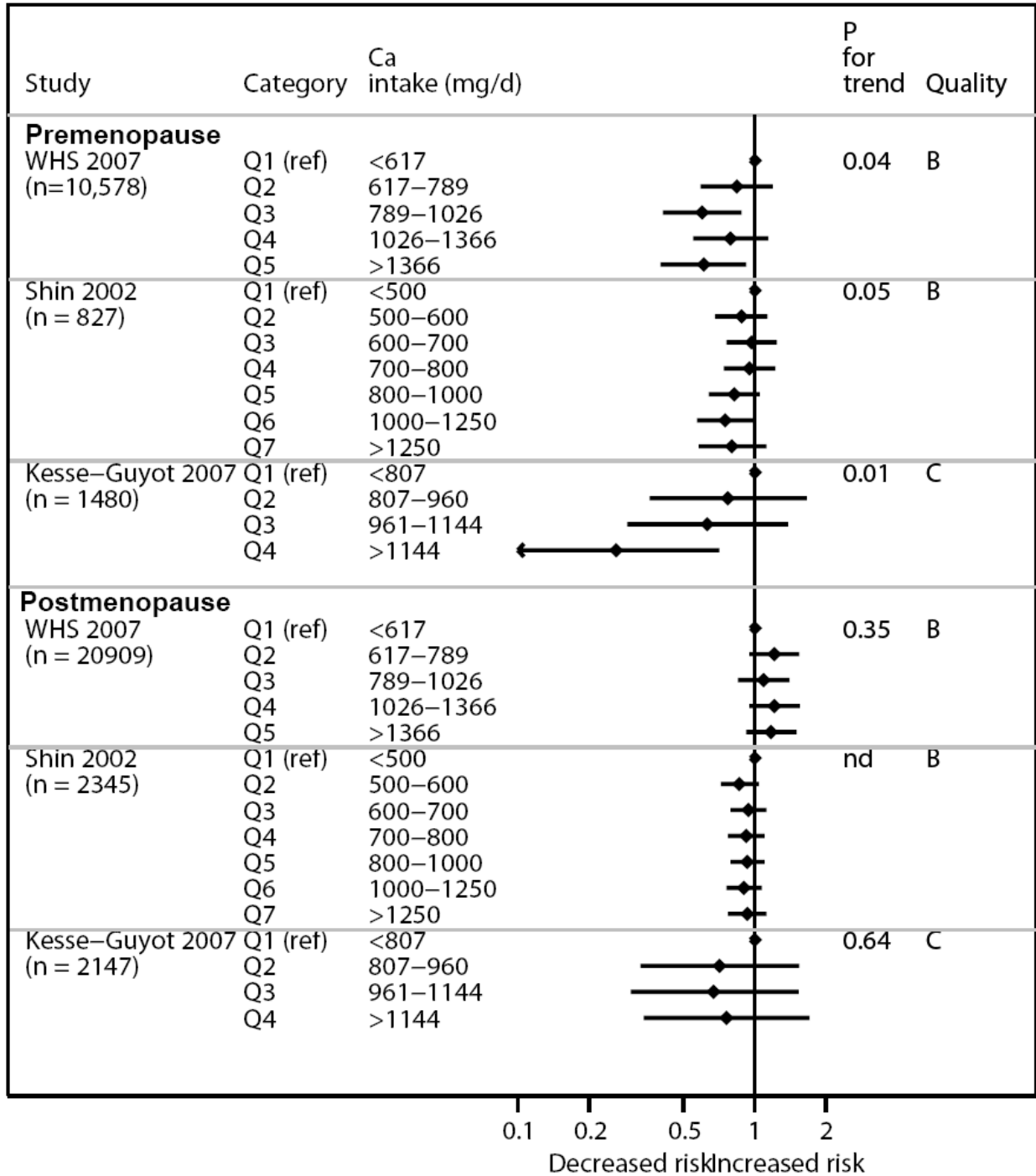
continued

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

HR: hazard ratio

*Statistically significant (P<0.05)

Figure 20. Breast cancer risk stratified by calcium intake



Breast Mammographic Density.

Synopsis.

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

Detailed presentation (Tables 71 & 72).

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

Findings by age and sex.

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

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|---|------------------------|---|--|--|---------|---------|-------------|-----------|----------|---|---|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Cohort | | | | | | | | | | | | |
| Mishra 2008 ¹⁷¹ Medical MRC NSHD UK 54° N [18827811] | <ul style="list-style-type: none"> Health status Mean age (range/SD), y | No breast cancer 52 | <ul style="list-style-type: none"> Dietary assessment method Internal validation? (y/n) | 5-day food diaries McCance and Widdowson's food table ND | At age 36 y: <523, 524-648, 652-784, 785-940, >941 At age 43 y: <611, 612-735, 736-859, 860-1020, >1021 | x | x | x | x | | x | Total calcium intake from diet and supplement |

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

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

Pancreatic cancer.

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

Synopsis.

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

Detailed presentation (Tables 73 & 74).

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

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

Findings by life stage.

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

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

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

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

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

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

Calcium and pregnancy-related outcomes

Preeclampsia.

Synopsis.

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

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

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

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

Detailed presentation (Tables 75, 76 & 77).

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

We identified five systematic reviews¹⁷³⁻¹⁷⁷ (with meta-analyses) of RCTs on calcium supplementation in the first or second trimester versus placebo for the prevention of preeclampsia (Appendix D). We selected a 2006 Cochrane review as eligible for this section.¹⁷⁶ All other systematic reviews were covered by the Cochrane review. We did not identify any RCTs published after the Cochrane review was conducted.

Eligible were RCTs comparing at least 1000 mg/d of calcium versus placebo in pregnant women. Studies were performed in several countries (both developed and developing). The review defined preeclampsia as high gestational blood pressure (diastolic blood pressure >90 mmHg, or increase more than 15 mm Hg in diastolic or more than 30 mm Hg in systolic blood pressure) with significant proteinuria (at least 300 mg/d or at least 500 mg).¹

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

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

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

More than 80 percent of the total number of randomized women in this meta-analysis (n=12,914) came from two large trials that reported no significant effects of calcium supplementation for preeclampsia (RR=0.95, 95 percent CI 0.89, 1.05; by fixed effects synthesis). Based on their combined confidence interval, these two studies exclude modest and large effects of calcium for preeclampsia prevention. The remaining (smaller) trials show a protective effect. One of the large RCTs was performed in populations with low background calcium diets¹⁷⁸ and the other in populations with adequate background calcium diets.¹⁷⁹

Allowing for the above, there is no clear explanation for the observed discrepant findings across the trials in the systematic review. The recurrent pattern is that large trials showed no effect for calcium supplementation, whereas smaller trials showed large effects. Calcium supplementation for preeclampsia prevention is a well known example where large trials and smaller trials show systematically different effects. Past methodological explorations (before the publication of the WHO trial¹⁷⁸) have hypothesized that effects may be observed mostly among women with low calcium in their background diet.¹⁸⁰ However, as mentioned above, this is not supported by the subgroup analyses.

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

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Hofmeyr 2006 ¹⁷⁶ [16855957] | | |
| Design (Search Years) | Randomized controlled trials (1988-2006) | | |
| Population | Pregnant women less than 35 weeks of gestation regardless of their risk of hypertensive of pregnancy or their previous calcium intake | | |
| Intervention (Exposure) and Comparator | Calcium supplement (at least 1000 mg/d) vs. placebo | | |
| Results | <p>12 trials (n=15,528)^A</p> <p><i>Preeclampsia (mother):</i></p> <ul style="list-style-type: none"> All 12 trials (n=15,528): RR=0.48 (0.33, 0.69)^B; statistically heterogeneous Among 4 trials (n=5022) with adequate Ca in diet: RR=0.62 (0.32, 1.20); statistically heterogeneous Among 7 trials (n=10,154) with low Ca in diet: RR=0.36 (0.18, 0.70); statistically heterogeneous Among 5 trials (n=587) at high risk for hypertension: RR=0.22 (0.12, 0.42); statistically homogeneous Among 6 trials (n=14,619) at low risk for hypertension: RR=0.68 (0.49, 0.94); statistically heterogeneous <p><i>High blood pressure with or without proteinuria (mother):</i></p> <ul style="list-style-type: none"> Among 11 trials (n=14,946): RR= 0.70 (95% CI 0.57, 0.86); statistically heterogeneous Among 4 trials (n=5022) with adequate Ca in diet: RR=0.90 (0.81, 0.99); statistically homogeneous Among 6 trials (n=9684) with low Ca in diet: RR=0.47 (0.29, 0.76); statistically heterogeneous Among 4 trials (n=327) at high risk for hypertension: RR=0.47 (0.22, 0.97); statistically heterogeneous Among 7 trials (n=14,619) at low risk for hypertension: RR=0.78 (0.64, 0.95); statistically heterogeneous <p><i>Preterm birth:</i></p> <ul style="list-style-type: none"> Among 10 trials (n=14,751): RR = 0.81 (0.64, 1.03); statistically heterogeneous Among 4 trials (n=5033) with adequate Ca in diet: RR=0.59 (0.26, 1.33); statistically heterogeneous Among 6 trials (n=9684) with low Ca in diet: RR=0.90 (0.80, 1.02); statistically homogeneous Among 4 trials (n=478) at high risk for hypertension: RR=0.45 (0.24, 0.83); statistically homogeneous Among 7 trials (n=14,183) at low risk for hypertension: RR=0.91 (0.74, 1.12); statistically heterogeneous <p><i>Small for gestational age (infant):</i></p> <ul style="list-style-type: none"> Among 3 trials (n=13,091; fixed effects): RR = 1.10 (0.88, 1.37); statistically homogeneous | | |
| Comments | About 80% of participants are from two well designed and well conducted RCTs. ^{178,179} The two large RCTs show no effects for all four outcomes. | | |
| AMSTAR Criteria | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | Yes |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | No |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | | |

^A RR <1.0 favors calcium supplementation

^B 95% confidence interval

Cohort studies.

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

Findings by life stage.

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

Table 76. Calcium and preeclampsia and other pregnancy outcomes: Characteristics of cohort studies^{A,B}

| Author Year Study Name Location (Latitude) [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Outcomes and Comments | | |
|---|---|--|---|--|---|---------|---------|-------------|-----------|--------------------------|---|-----------------|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Morris 2007 ¹⁸¹ CPEP reanalysis ^C US (various) [11262466] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | Healthy ND 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | | X | X | | | X | Total Ca (both) |
| Oken 2007 ¹⁸² Project Viva US (42°N) [17521921] | <ul style="list-style-type: none"> • Health status • Mean age (SD), y • Male (%) | Healthy [most 30 to <40] 0 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome as a function of Ca intake | | X | X | | | | Total Ca (both) |

^A Both table entries are treated as cohort studies.

^B In contrast with most other summary tables of study characteristics, this table is ordered alphabetically by study author.

^C Reanalysis of the CPEP trial (calcium versus placebo) for preeclampsia prevention focusing on calcium content in diet (and including the intervention dose in the analyses)

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

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

^A Excludes 119 women with pregnancy-induced hypertension – comparison versus normotensive women

^B Per 300 mg of Ca intake (from supplement or diet)

^C Excludes 59 women with preeclampsia – comparison versus normotensive women

High blood pressure with or without proteinuria during pregnancy.

Synopsis.

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

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

Detailed presentation (Tables 75, 76 & 77).

Relevant published systematic reviews (with meta-analyses).

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

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

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

Cohort studies.

A single prospective cohort study¹⁸² (Table 68) reported no association between calcium intake levels and risk for preeclampsia.¹⁸² (See Table 69.)

Findings by life stage.

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

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

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

Preterm birth.

Synopsis.

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

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

Detailed presentation (Table 75).

Relevant published systematic reviews (with meta-analyses).

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

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

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

Findings by life stage.

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

Small for gestational age infant.

Synopsis.

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

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

Detailed presentation (Table 75).

Relevant published systematic reviews (with meta-analyses).

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

Findings by life stage.

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

Calcium and all-cause Mortality

Synopsis.

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

Detailed presentation (Tables 78 & 79).

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

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

Findings by life stage.

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

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

| Author Year Study Name Location (Latitude) [PMID] | Population | Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|--|---|--|---|--|---|---------|---------|-------------|-----------|----------|---|-----------------|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Van der Vijver 1992 ¹⁰⁵ & Slob 1993 ¹²⁶ Netherlands (52°N) [1544755 & 8478144] | <ul style="list-style-type: none"> • Health status • Age range, y • Male (%) | General population 40-65y 51 | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Outcome stratified by total Ca intake quintiles | X | X | X | | | X | Total Ca (food) |

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

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

Calcium and Hypertension and Blood Pressure

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

Calcium and hypertension.

Synopsis.

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

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

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

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

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

Findings per calcium intake level.

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

Findings per age and sex.

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

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

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

Findings by life stage.

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

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

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

| Author Year Study Name Location [PMID] | Population | Dietary Calcium intake | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments | | |
|---|--|--------------------------------|---|--|---|---------|---------|-------------|-----------|----------|---|-----------------|
| | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | | | |
| Alonso 2005 ¹⁸³ U Navarra Follow-up Navarra Spain (43°N) [16280427] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Normo-tensive 36 (20-90) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Hypertension incidence stratified by total Ca intake quintiles | X | X | X | X | | X | Total Ca (both) |
| Dwyer 1996 ^{184A} NHANES I US (various) [8890661] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Normo-tensive 46 (25-74) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | 24 hr recall nd | Hypertension incidence stratified by total Ca intake quartiles | X | X | X | | | X | Total Ca (both) |
| Ascherio 1992 ¹⁸⁵ HPFS US (various) [1330360] | <ul style="list-style-type: none"> • Health status • Median age (range), y • Male (%) | Normo-tensive 50 (40-75) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Hypertension incidence stratified by total Ca intake categories | | X | X | | | X | Total Ca (both) |
| Ford 1991 ^{186B} NHANES I US (various) [1937662] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Normo-tensive nd (≥25) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | nd nd | Hypertension incidence stratified by total Ca intake quartiles | X | X | | | | | Total Ca (both) |
| Wang 2008 ¹⁸⁷ WHS US (various) [18259007] | <ul style="list-style-type: none"> • Health status • Mean age (SD, range), y • Male (%) | Normo-tensive 54 (6.5; ≥45) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ No | Hypertension incidence stratified by total Ca intake quintiles | X | X | X | X | | X | Total Ca (both) |
| Ascherio 1996 ¹⁸⁸ NHS US (various) [8621198] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Normo-tensive nd (30-55) | <ul style="list-style-type: none"> • Dietary assessment method • Internal validation? (y/n) | FFQ Yes | Hypertension incidence stratified by total Ca intake categories | | X | X | | | X | Total Ca (both) |

^A Overall and age subgroup analyses from NHANES I reported in this study. However, different samples selected; 63% male.

^B Sex and race subgroup analyses from NHANES I reported in this study. However, different samples selected; 35% male.

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

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

continued

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

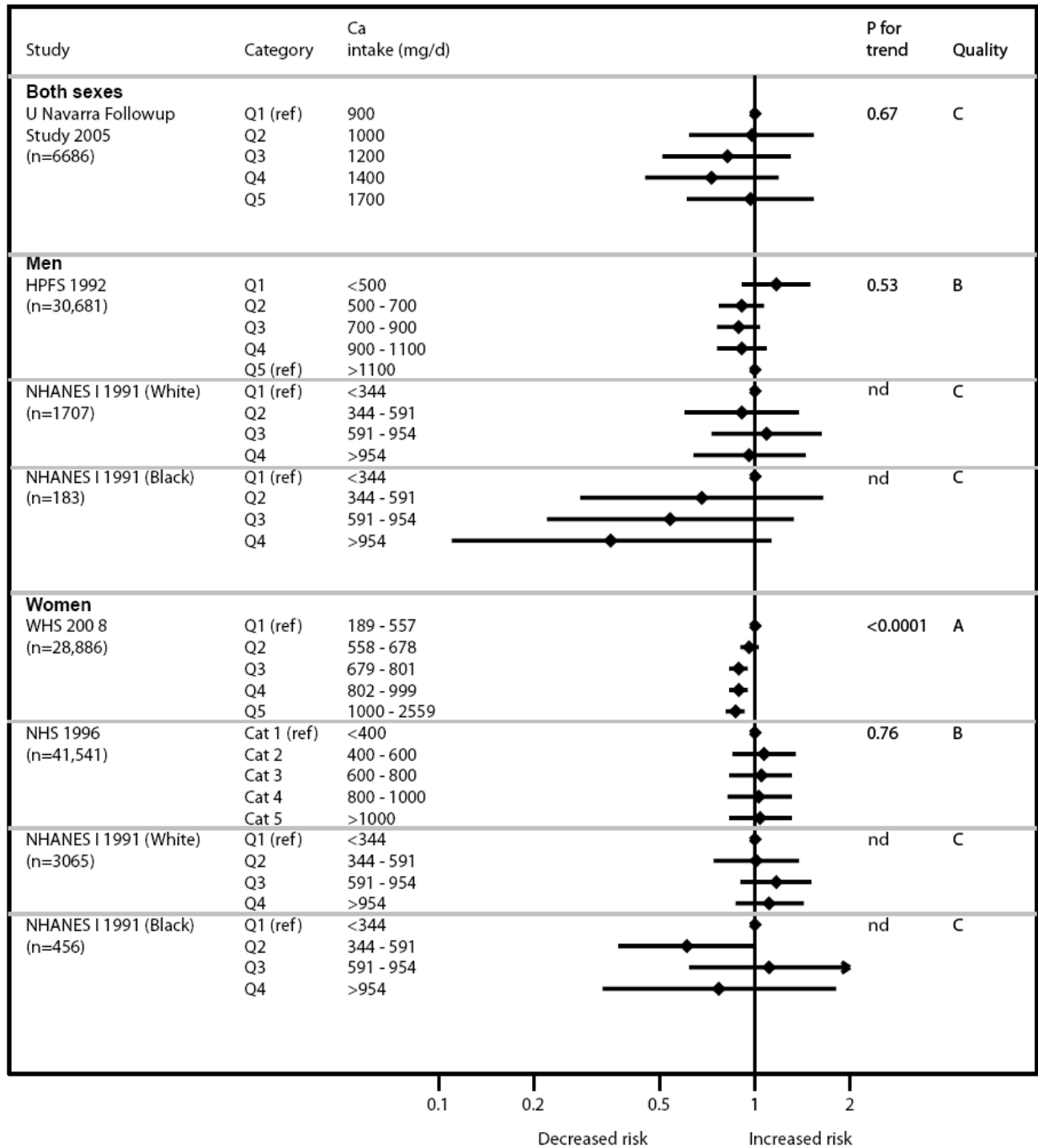
* Statistically significant (P<0.05)

^A Overall and age subgroup analyses from NHANES I reported in this study. However, different samples selected; 63% male.

^B Sex and race subgroup analyses from NHANES I reported in this study. However, different samples selected; 35% male.

^C Estimated from available data

Figure 21. Hypertension risk stratified by calcium intake



Calcium and blood pressure.

Synopsis.

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

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

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

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

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

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

The six systematic reviews explicitly or implicitly used generally different eligibility criteria, resulting in large overlaps in the trials included.^{169,189-193} The systematic reviews included a total of 64 trials. The largest systematic review¹⁸⁹ included trials up to 1997 and was an update of a previous review¹⁹¹ that reported more analyses. The next largest systematic review¹⁹⁰ was one of the more recent systematic reviews (including trials through 2003). The most recent systematic review¹⁶⁹ was restricted to trials of people with hypertension. Five more recent trials, not included in any of the systematic reviews were found.^{120,194-197} Two of the trials were restricted to normotensive individuals; none included only people with hypertension.

Normotensive individuals.

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

Findings per calcium intake level.

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

Findings per age and sex.

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

Hypertensive individuals.

Four systematic reviews evaluated trials of hypertensive individuals (Bucher et al. 1996¹⁹¹, Allender et al. 1996¹⁹², Cappuccio et al. 1989¹⁹³, and Dickinson 2006¹⁹⁸). Dickinson et al. (2006) included only studies of people with hypertension. The range of supplemental calcium was approximately 400 to 2000 mg/d in most systematic reviews, with most studies using 1000 to 1500 mg/d. The systematic reviews generally found significant effects on systolic blood pressure of about -2 to -4 mm Hg, but no (or small) effects on diastolic blood pressure. The one systematic review that found no effect of calcium supplementation on systolic blood pressure (Cappuccio et al. 1989) was the oldest systematic review (including trials up to only 1988). In addition, the reviewers were highly selective in their eligibility criteria, having excluded trials that did not report various types of baseline data. The one systematic review that found a significant effect of calcium supplementation on diastolic blood pressure (Bucher et al. 1996) meta-analyzed only 6 trial subgroups of people with hypertension, compared to 10 to 16 trials in the other systematic reviews. None of the more recent trials provided analyses in only people with hypertension.

Findings per calcium intake level.

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

Findings per age and sex.

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

All trials (combined normotensive and hypertensive individuals).

Five systematic reviews (including one which is an update of a second) combined trials of hypertensive, normotensive, or mixed groups of people (Griffith et al. 1999¹⁸⁹, van Mierlo et al. 2006¹⁹⁰, Bucher et al. 1996¹⁹¹, Allender et al. 1996¹⁹², and Cappuccio et al. 1989¹⁹³). The range of calcium supplementation was approximately 400 to 2000 mg/d in most systematic reviews, with most studies using 1000 to 1500 mg/d. The systematic reviews generally found a significant effect of calcium supplementation on systolic blood pressure of -0.9 to -1.9 mm Hg (excluding the earliest, highly selective systematic review by Cappuccio et al. (1989)¹⁹³, as discussed above). The two systematic reviews that included the most studies (Griffith et al. 1999¹⁸⁹ and van Mierlo et al. 2006¹⁹⁰) found a significant effect on diastolic blood pressure (-0.8 and -1.0 mm Hg, respectively). The smaller, older systematic reviews found no significant effect (Allender et al. 1996¹⁹² and Cappuccio et al. 1989¹⁹³). The reason for the difference in conclusions of the systematic reviews may relate to greater statistical power in the more recent meta-analyses or differences in study eligibility criteria. The systematic reviews that reported on study heterogeneity found significant heterogeneity. Three of the systematic reviews reported data on subgroup or regression analyses to explain the heterogeneity. The only factor that explained a significant amount of the heterogeneity was the difference in effect between studies of people with or without hypertension. (The age, sex, and calcium dose analyses are described below.)

Two recent randomized trials included postmenopausal women (over 50 or 55 years) regardless of their blood pressure;^{120,194} a third trial enrolled pregnant women and evaluated long-term postpartum blood pressures.¹⁹⁶ The trials each compared different interventions: calcium citrate 1000 mg versus placebo; dairy product intake (with a mean of 1242 mg/d calcium) versus nondairy product intake (377 mg/d calcium); and calcium carbonate 2000 mg/d versus placebo in women all taking prenatal vitamins that included 400 IU/d vitamin D₂. The calcium citrate trial was of methodological quality B; the other two trials C. The recent trials found broadly similar conclusions to that of the systematic reviews, with women with greater calcium intake having lower systolic blood pressure (-2.2 to -5.4 mm Hg) and smaller decreases in diastolic blood pressure (-0.7 to -2.2 mm Hg); though none of the effects was statistically significant.

Findings per calcium intake.

Three systematic reviews¹⁹⁰⁻¹⁹² evaluated calcium dose (or intake) as a source of heterogeneity. None found a significant association. Specifically, van Mierlo et al. (2006) found similar (though smaller) effects in studies of over 1000 mg/d of calcium (SBP/DBP -1.75/-0.56) compared to studies of 1000 mg/d of calcium or less (-2.17/-1.41).

Findings per age and sex.

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

Findings by life stage.

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

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

| Author Year [PMID] | Griffith 1999 ¹⁸⁹ [10075392] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|--|---|--|-----|--|-----|-----|-----------|----------------------|----------------------|-------|----------------------|----------------------|-----------|----------------------|----------------------|------|----------------------|----------------------|--------------------------|----------------------|----------------------|---------------|----------------------|----------------------|------------------|----------------------|----------------------|----------|----------------------|----------------------|
| Design (Search Years) | Randomized controlled trials (1966-1997) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 600-2000 mg (36% 1000 mg; 26% 1500-1600 mg; 12% 2000 mg) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Results | 42 trials SBP: -1.44 (-2.20, -0.68) ^A ; statistically heterogeneous DBP: -0.84 (-1.44, -0.24); statistically heterogeneous Subgroup analyses did not find that heterogeneity could be explained by age, sex, baseline calcium, dietary versus nondietary calcium, or quality. Subgroups with hypertensive versus normotensive people were significantly different (no further details). Conclusions similar to previous systematic review (Bucher 1996 ¹⁹¹) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comments | Update of Bucher 1996 ¹⁹¹ (see below). | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| AMSTAR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| All publication types and languages included? | Yes | Publication bias assessed? | No | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | No | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study characteristics provided? | Yes | Study quality not discussed in conclusions. Funding source reported, but not conflict of interest. | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Author Year [PMID] | van Mierlo 2006 ¹⁹⁰ [16673011] | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Design (Search Years) | Randomized controlled trials (1966-2003) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Intervention and Comparator | Calcium supplementation versus placebo (no supplement) Dose range 355-2000 mg (40% 1000 mg; 32% 1500-1600 mg; 6% 2000 mg) | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Results | 40 trials SBP: -1.86 (95% CI -2.91, -0.81); statistically heterogeneous DBP: -0.99 (95% CI -1.61, -0.37); statistically heterogeneous In multivariable analysis including age, sex, initial calcium intake, calcium dose, and initial blood pressure: <table border="1" style="margin-left: 20px; width: 100%;"> <thead> <tr> <th></th> <th>SBP</th> <th>DBP</th> </tr> </thead> <tbody> <tr> <td>Age <45 y</td> <td>-1.45 (-2.99, +0.09)</td> <td>-1.26 (-2.20, -0.33)</td> </tr> <tr> <td>≥45 y</td> <td>-2.33 (-3.69, -0.96)</td> <td>-0.80 (-1.62, +0.02)</td> </tr> <tr> <td>Male ≤50%</td> <td>-2.20 (-3.68, -0.72)</td> <td>-1.12 (-1.98, -0.26)</td> </tr> <tr> <td>>50%</td> <td>-1.77 (-3.13, -0.42)</td> <td>-0.84 (-1.65, -0.04)</td> </tr> <tr> <td>Initial BP <140/90 mm Hg</td> <td>-2.04 (-3.40, -0.68)</td> <td>-1.04 (-1.86, -0.22)</td> </tr> <tr> <td>≥140/90 mm Hg</td> <td>-1.85 (-3.45, -0.32)</td> <td>-0.89 (-1.79, +0.01)</td> </tr> <tr> <td>Ca dose ≤1000 mg</td> <td>-2.17 (-3.59, -0.75)</td> <td>-1.41 (-2.24, -0.59)</td> </tr> <tr> <td>>1000 mg</td> <td>-1.75 (-3.20, -0.31)</td> <td>-0.56 (-1.40, +0.29)</td> </tr> </tbody> </table> Blood pressures not statistically significantly different between any strata. | | | | 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) |
| | 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) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comments | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| AMSTAR | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| All publication types and languages included? | Unclear | Publication bias assessed? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Included and excluded studies listed? | Partial | Conflicts of interest stated? | Yes | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Study characteristics provided? | Yes | No data on inclusion of unpublished data. Excluded studies available from authors | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

Table 82. continued

| | | | | | | | | | |
|--|--|---|-----|---------------|--------------------------|--------------------------|---------------|--------------------------|--------------------------|
| Author Year [PMID] | Bucher 1996 ¹⁹¹ [8596234] | | | | | | | | |
| Design (Search Years) | Randomized controlled trials (1966-1994) | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation vs. placebo (no supplement) Dose range 406-2000 mg (41% 1000 mg; 31% 1500-1600 mg; 8% 2000 mg) | | | | | | | | |
| Results | 33 trials [Overall summary results were updated in Griffith 1999 ¹⁸⁹ , above] Studies with specified subgroups of hypertensive and normotensive participants (6 trials): <table border="0" style="width: 100%;"> <tr> <td style="padding-right: 20px;">Hypertensives</td> <td style="padding-right: 20px;">SBP -4.30 (-6.47, -2.13)</td> <td>DBP -1.50 (-2.77, -0.23)</td> </tr> <tr> <td>Normotensives</td> <td>SBP -0.27 (-1.80, +1.27)</td> <td>DBP -0.33 (-1.56, +0.90)</td> </tr> </table> 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. | | | 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) |
| 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) | | | | | | | |
| Comments | Updated in Griffith 1999 ¹⁸⁹ (see above) | | | | | | | | |
| AMSTAR | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes | | | | | | |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | Yes | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes | | | | | | |
| All publication types and languages included? | Yes | Publication bias assessed? | No | | | | | | |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | No | | | | | | |
| Study characteristics provided? | Yes | Funding source reported, but not conflict of interest. | | | | | | | |
| Author Year [PMID] | Allender 1996 ¹⁹² [8610952] | | | | | | | | |
| Design (Search Years) | Randomized controlled trials (1982-1993) | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation vs. placebo (no supplement) Dose range 400-2160 mg (35% 1000 mg; 29% 1500-1600 mg; 10% 2000 mg) | | | | | | | | |
| Results | 26 trials (22 trials included in meta-analyses) SBP: -0.89 (-1.74, -0.05) DBP: -0.18 (-0.75, +0.40) <table border="0" style="width: 100%;"> <tr> <td style="padding-right: 20px;">Hypertensives</td> <td style="padding-right: 20px;">SBP -1.68 (-3.18, -0.18)</td> <td>DBP +0.02 (-0.96, +1.00)</td> </tr> <tr> <td>Normotensives</td> <td>SBP -0.53 (-1.56, +0.49)</td> <td>DBP -0.28 (-0.99, +0.42)</td> </tr> </table> By weighted linear regression analyses, age, sex, calcium dose, trial duration were not associated with treatment effect (P>0.10) | | | 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) |
| 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) | | | | | | | |
| Comments | | | | | | | | | |
| AMSTAR | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | No | | | | | | |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | No | | | | | | |
| All publication types and languages included? | Yes | Publication bias assessed? | No | | | | | | |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No | | | | | | |
| Study characteristics provided? | Yes | Excluded studies not enumerated or listed. Fixed effects models used. | | | | | | | |
| Author Year [PMID] | Cappuccio 1989 ¹⁹³ [2697729] | | | | | | | | |
| Design (Search Years) | Randomized controlled trials (1983-1988) | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | |
| Intervention and Comparator | Nondietary calcium supplementation versus placebo (no supplement) or low calcium intake Dose range 800-1600 mg (60% 1000 mg; 27% 1500-1600 mg) | | | | | | | | |
| Results | 15 trials SBP (supine): -0.13 (-0.46, +0.19) DBP (supine): +0.03 (-0.17, +0.22) <table border="0" style="width: 100%;"> <tr> <td style="padding-right: 20px;">Hypertensives</td> <td style="padding-right: 20px;">SBP +0.06 (-0.59, +0.72)</td> <td>DBP +0.03 (-0.21, +0.27)</td> </tr> </table> | | | Hypertensives | SBP +0.06 (-0.59, +0.72) | DBP +0.03 (-0.21, +0.27) | | | |
| Hypertensives | SBP +0.06 (-0.59, +0.72) | DBP +0.03 (-0.21, +0.27) | | | | | | | |
| Comments | | | | | | | | | |
| AMSTAR | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | No | | | | | | |
| Two independent reviewers? | nd | Study quality appropriately used in analysis? | NA | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | No | | | | | | |
| All publication types and languages included? | nd | Publication bias assessed? | No | | | | | | |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No | | | | | | |
| Study characteristics provided? | Yes | Excluded studies not enumerated or listed. Fixed effects models used. | | | | | | | |

Table 82. continued

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Dickinson 2006 ¹⁹⁸ [16625609] ^B | | |
| Design (Search Years) | Randomized controlled trials (1982-2003/2005 ^C) | | |
| Population | Hypertensive participants | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2000 mg (50% 1000 mg; 25% 1500-1600 mg; 6% 2000 mg) | | |
| Results | 13 trials SBP: -2.53 (-4.45, -0.60); statistically heterogeneous DBP: -0.81 (-2.07, +0.44); statistically heterogeneous Ca dose <1200 mg SBP -2.67 (-5.15, -0.18) DBP -0.75 (-2.13, +0.63) Ca dose 1200-2000 mg SBP -2.69 (-5.86, +0.47) DBP -0.78 (-3.82, +2.25) Not statistically significantly different by calcium dose | | |
| Comments | AMSTAR | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | Yes |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | Yes |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | | |

^A Numbers in parentheses are 95% confidence intervals

^B A technical update, with no further studies added was published in the Cochrane database in 2008.

^C Different dates for different databases.

Table 83. Calcium and blood pressure: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|---|--|---------------------------|--|--|
| Whelton 1997 ¹⁹⁵ TOHP US (various) [9022561] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | No HTN (DBP 80-89 mm Hg) 43 (30-54) 68 | nd | Calcium supplement vs. Placebo | nd |
| Lijnen 1995 ¹⁹⁷ Leuven, Belgium (51°N) [8557965] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Normotensive 24 (20-44) 100 | "Low calcium diet" run-in | Calcium supplement vs. Placebo | nd With low dairy intake |
| Reid 2005 ¹⁹⁴ Auckland, New Zealand (36.5°S) [15827103] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Healthy 75 (≥55) 0 | Ca 857 mg/day | Calcium supplement vs. Placebo | Calcium group: 55%, Placebo group: 58% |
| Ghadirian 1995 ¹²⁰ Montreal, Canada (46°N) [7493659] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Healthy ~80 (≥50) 0 | Ca 776 mg/day | Dairy vs. Dairy-free intake | Non-compliant and those who provided incomplete data were excluded. |
| Hatton 2003 ¹⁹⁶ CPEP Portland, Oregon (45.5°N) [14553957] | <ul style="list-style-type: none"> • Health status • Mean age (range/SD), y • Male (%) | Pregnant during trial nd 0 | nd | Calcium supplement vs. Placebo (both on prenatal vitamins including Vit D ₂ 400 IU) | nd (but all had to meet a compliance test prior to randomization) Oregon site only. Post-pregnancy followup |

Table 84. Calcium and blood pressure: Results of RCTs

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

continued

| Author Year Study Name [PMID] | Age Range, Sex; Population | Outcome | 1°/2° | Mean Followup, unit | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|---|---|---------|-------|---------------------------|---|-----------------|----------|----------|--------|------------------|--------------------|------------------------|----------|------------------|
| Ghadirian 1995 ¹²⁰ Canada [7493659] | ≥50 y, Women; All BP | DBP | 2° | 1 mo | Dairy intake (1242 mg Ca) | 81 | mm Hg | 81.17 | -7.78 | -10.0, -5.5* | -2.2 | -5.4, 1.0 ^C | NS | C |
| | | | | | Dairy-free (377 mg Ca) | 77 | | 79.09 | -5.59 | -7.9, -3.3* | | | | |
| Hatton 2003 ¹⁹⁶ CPEP [14553957] | Pregnant, Women ^B ; All BP | DBP | 2° | 2 y post- partum | Ca carbonate 2000 mg (+Vit D ₂ 400 IU) | 37 | mm Hg | nd | | Final 67.1 | Difference -0.7 | -4.8, 3.4 | NS | C |
| | | | | | Placebo (+Vit D ₂ 400 IU) | 25 | | nd | | 67.8 | | | | |

^A From figure

^B Blood pressure outcomes are 1 year post-partum

^C Estimated from available data

Combined Vitamin D and Calcium and Health Outcomes

Women's Health Initiative (WHI) trial.

The WHI trial provided data for numerous health outcomes of interest. For this reason and because of some methodological issues unique to this trial, the study is discussed here. The trial compared combined vitamin 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 Calcium and Growth

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

Synopsis.

One C-rated nonrandomized study compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth.

Detailed presentation (Tables 4 & 6).

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

We identified a study from India that included a nonrandomized comparison between combined vitamin D (1200 IU/d) and calcium (375 mg/d) for the expectant mothers versus no supplementation. The outcome was infant birth weight.⁴¹ This study has already been described in the "Vitamin D and growth" section, as it also included a vitamin D only intervention arm. The study included expectant mothers with daily milk intake less than 500 mL and estimated daily vitamin D intake less than 30 IU. It was rated C for methodological quality, because of the lack of randomization and incomplete reporting of analyses. According to the reported analysis,

infants of women who received supplementation were significantly heavier at birth by 160 g on average (95 percent CI 0, 320).

Findings by life stage

- **0 – 6 mo** One C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth by 160 g on average (95 percent CI 0, 320). (See also the Pregnant & lactating women.)
- **7 mo – 2 y** No identified study covered this life stage.
- **3 – 8 y** No identified study covered this life stage.
- **9 – 18 y** No identified study covered this life stage.
- **19 – 50 y** Not reviewed
- **51 – 70 y** Not reviewed
- **≥71 y** Not reviewed
- **Postmenopause** Not reviewed
- **Pregnant & lactating women** One C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth by 160 g on average (95 percent CI 0, 320). (See also the 0 – 6 mo category.)

Combined Vitamin D and Calcium and Cardiovascular Disease

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and cardiovascular events. A variety of cardiovascular events after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined daily vitamin 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.

Detailed presentation (Tables 85 & 86).

In the WHI trial, discussed above, the evaluated cardiovascular outcomes were all prespecified secondary outcomes.^{199,200} On average, the women had normal blood pressure. There were no significant effects of the supplementation on any of the outcomes, though three of the outcomes did approach statistical significance suggesting increased events with supplementation: composite cardiac events (HR = 1.08 [95 percent CI 0.99, 1.19]), coronary artery bypass grafting or percutaneous coronary interventions (HR=1.09 [95 percent CI 0.98, 1.22]), and transient ischemic attacks (HR=1.16 [95 percent CI 0.95, 1.42]). The authors, however, concluded that calcium and vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy postmenopausal women. The outcomes cardiac death and stroke were evaluated by age decade. No interaction was found with age (no significant difference across age groups). A similar analysis based on total calcium intake (dietary plus supplemental) also found no interaction.

Findings per intake level.

No conclusions are possible about a dose effect from this single study, especially since the women were allowed to take additional concurrent calcium and vitamin D supplements. However, no interaction was found with total reported calcium intake.

Findings by age and sex.

The study investigated postmenopausal women 50 to 79 years old. No interaction of effects with decade of age was found.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data available

- **51 – 70 y** One large trial that included women mostly within this life stage (WHI) found no significant effect of combined vitamin 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 85. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|---|--|--|-----------------|
| Hsia 2007 ¹⁹⁹ LaCroix 2009 ²⁰⁰ WHI US (various) [17309935 19221190] | <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 page 242 |

Table 86. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality | |
|--|-------------------|---|-------|---------------------|------------------------------|---|------------|--------------------------------|------------|------------|------------|------------------|------|
| Hsia 2007 ¹⁹⁹ LaCroix 2009 ²⁰⁰ WHI [17309935 19221190] | 50-79 y, Women | Cardiovascular death | 2° | 7 | Vit D + Ca | 226 | 18,176 | HR (Suppl/Placebo) | 0.92* | 0.77, 1.10 | NS | B | |
| | | | | | Placebo | 244 | 18,106 | | | | | | |
| | | Cardiac composite (MI, CHD death, CABG, or PCI) | 2° | | | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 920 | 18,176 | HR | 1.08 | 0.99, 1.19 | | 0.10 |
| | | Placebo | 841 | 18,106 | | | | | | | | | |
| | | Cardiac composite (MI or CHD death) | 2° | | | Vit D + Ca | 499 | 18,176 | HR | 1.04 | 0.92, 1.18 | | 0.50 |
| | | Placebo | 475 | 18,106 | | | | | | | | | |
| | | CHD death | 2° | | | Vit D + Ca | 130 | 18,176 | HR | 1.01* | 0.79, 1.29 | | 0.92 |
| | | Placebo | 128 | 18,106 | | | | | | | | | |
| | | MI | 2° | | | Vit D + Ca | 411 | 18,176 | HR | 1.05 | 0.91, 1.20 | | 0.52 |
| | | Placebo | 390 | 18,106 | | | | | | | | | |
| | | CABG or PCI | 2° | | | Vit D + Ca | 674 | 18,176 | HR | 1.09 | 0.98, 1.22 | | 0.12 |
| | | Placebo | 607 | 18,106 | | | | | | | | | |
| | | Hospitalized for heart failure | 2° | | | Vit D + Ca | 394 | 18,176 | HR | 0.95 | 0.83, 1.10 | | 0.50 |
| | | Placebo | 407 | 18,106 | | | | | | | | | |
| | | Angina | 2° | | | Vit D + Ca | 404 | 18,176 | HR | 1.08 | 0.94, 1.24 | | 0.30 |
| | | Placebo | 377 | 18,106 | | | | | | | | | |
| | | Cerebrovascular composite (Stroke or TIA) | 2° | | | Vit D + Ca | 563 | 18,176 | HR | 1.02 | 0.91, 1.15 | | 0.75 |
| | | Placebo | 547 | 18,106 | | | | | | | | | |
| | | Stroke | 2° | | | Vit D + Ca | 362 | 18,176 | HR | 0.95 | 0.82, 1.10 | | 0.51 |
| | | Placebo | 377 | 18,106 | | | | | | | | | |
| TIA | 2° | | | Vit D + Ca | 213 | 18,176 | HR | 1.16 | 0.95, 1.42 | 0.13 | | | |
| Placebo | 182 | 18,106 | | | | | | | | | | | |
| Cerebrovascular death | 2° | | | Vit D + Ca | 213 | 18,176 | HR | 0.89* | 0.62, 1.29 | NS | | | |
| Placebo | 182 | 18,106 | | | | | | | | | | | |

Combined Vitamin D and Calcium and Body Weight

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

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and body weight in adults. One RCT each tested the effect of combined vitamin D and calcium in the setting of either an isocaloric diet or an energy restricted diet. Both used vitamin 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 87 & 88).

Isocaloric diet.

The WHI trial was analyzed for the effect of daily combined vitamin D₂ 400 IU and calcium carbonate 1000 mg on weight.²⁰¹ The trial included about 36,000 postmenopausal women aged 50 to 79 years. The methodological quality of the study was B. At 7 year followup, the net change in body weight (supplemented minus control) was -0.13 kg (95 percent CI -0.21, -0.05; less weight gained in supplement group). This was of questionable clinical significance, but was statistically significant. The investigators performed numerous subgroup analyses including those based on age. There were no substantive or statistically significant differences among the evaluated age subgroups.

Energy restricted diet.

A trial performed in Quebec City analyzed 63 premenopausal overweight or obese women (mean age 43) comparing daily vitamin D₂ 400 IU and calcium carbonate 1200 mg versus placebo.²⁰² Women in both study groups were placed on a weight-loss intervention which consisted of a 700 Kcal/day decrease in energy intake for 15 weeks; the women met biweekly with a nutritionist. The trial was rated methodological quality C due to a high drop out rate (25 percent) and poor description of the methodology. Women in both study groups on average lost weight, with those in the supplement group losing 1.0 kg more (4 vs. 3 kg). However, this effect was not statistically significant (P=0.19).

Findings per vitamin D and calcium dose.

No conclusion could be reached about a possible effect of vitamin D and calcium dose.

Findings per age and sex.

The trials included only women. The effect of supplementation on postmenopausal women not on an energy restricted diet was of questionable clinical significance after 7 years. The effect of supplementation for 15 weeks on overweight and obese premenopausal women (in an approximate age range of 32 to 54 years) on an energy restricted diet was relatively large (-4 vs. -3 kg), but this difference between the supplemented and control groups was not statistically significant.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** A single trial of women on an energy restricted diet found a nonsignificant difference in weight loss between that those assigned to vitamin D 300 IU and calcium 1200 mg supplementation for 15 weeks.
- **51 – 70 y** The WHI trial found no clinically significant effect on weight of vitamin D 300 IU and calcium 1000 mg after 7 years.
- **≥71 y** The subgroup of women in the WHI trial in this life stage had a similar net weight change as all the study participants as a whole, but the effect was not statistically significant.
- **Postmenopause** All the women in the WHI trial were postmenopausal.
- **Pregnant & lactating women** Not reviewed

Table 87. Combined vitamin D and calcium and weight: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|---|---|--|----------------------------------|--|
| Caan 2007 ²⁰¹ WHI US (various) [17502530] | <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 page 242 Factorial design with HT vs. Placebo |
| Major 2007 ²⁰² 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 | Energy restriction |

Table 88. Combined vitamin D and calcium and weight: Results of RCTs

| Author Year Study Name [PMID] | Age Range, Sex (Subgp) | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|--|------------------------|---------|-------|-------------------------|--|--------------|------|----------|--------|---------------|--------------|-----------------|--------------------|---------------|
| Isocaloric Diet | | | | | | | | | | | | | | |
| Caan 2007 ²⁰¹ WHI [17502530] | 50-79 y, Women | Weight | 2° | 7 y | Vit D ₂ 400 IU + Ca carbonate 1000 mg | 18,129 | kg | 76.0 | nd | nd | -0.13 | -0.21, -0.05 | .001 ^A | B |
| | | | | | Placebo | 18,055 | | 75.9 | nd | nd | | | | |
| | (50-54 y) | | | | Vit D ₃ + Ca | 2592 | kg | nd | nd | | -0.24 | -0.45, -0.03 | <0.05 ^B | |
| | | | | | Placebo | 2561 | | nd | nd | | | | | |
| | (55-59 y) | | | | Vit D ₃ + Ca | 4134 | kg | nd | nd | | -0.08 | -0.24, +0.09 | NS | |
| | | | | | Placebo | 4135 | | nd | nd | | | | | |
| | (60-69 y) | | | | Vit D ₃ + Ca | 8276 | kg | nd | nd | | -0.15 | -0.27, -0.03 | <0.05 | |
| | | | | | Placebo | 8243 | | nd | nd | | | | | |
| | (70-79 y) | | | | Vit D ₃ + Ca | 3174 | kg | nd | nd | | -0.10 | -0.27, +0.09 | NS | |
| | | | | | Placebo | 2561 | | nd | nd | | | | | |
| | (White) | | | | Vit D ₃ + Ca | 15,047 | kg | nd | nd | | -0.13 | -0.22, -0.04 | <0.05 ^C | |
| | | | | | Placebo | 15,106 | | nd | nd | | | | | |
| | (Black) | | | | Vit D ₃ + Ca | 1682 | kg | nd | nd | | -0.32 | -0.59, -0.06 | <0.05 | |
| | | | | | Placebo | 1635 | | nd | nd | | | | | |
| (Hispanic) | | | | Vit D ₃ + Ca | 789 | kg | nd | nd | | -0.08 | -0.48, +0.32 | NS | | |
| | | | | Placebo | 718 | | nd | nd | | | | | | |
| (Asian / Pacific Islander) | | | | Vit D ₃ + Ca | 369 | kg | nd | nd | | +0.19 | -0.37, +0.75 | NS | | |
| | | | | Placebo | 353 | | nd | nd | | | | | | |
| Energy Restricted Diet | | | | | | | | | | | | | | |
| Major 2007 ²⁰² Quebec City, Canada [17209177] | 43 (SD) | Weight | 2° | 15 wk | Vit D ₂ 400 IU + Ca carbonate 1200 mg | 30 | kg | 81.5 | -4.0 | +9.0 | -1.0 | -2.31, +0.31 | 0.19 | C |
| | | | | | Placebo | 33 | | 83.6 | -3.0 | +11.7 | | | | |

^A In addition, subgroup analyses by baseline BMI and baseline dietary calcium intake are reported.

^B No statistically significant interaction with age.

^C No statistically significant interaction with ethnicity.

Combined Vitamin D and Calcium and Cancer

Cancer from all causes and total cancer mortality.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and total cancer incidence or mortality. Two RCTs reported different effects of combined vitamin D₃ and calcium supplementation on the risk of total cancer. The WHI showed no effects,⁷¹ while the trial conducted in Nebraska (latitude 41°N) reported significant reduction of risk of total cancer.⁵² However, both vitamin D doses and baseline vitamin D status were substantially different between these two RCTs. Therefore, the effects from these two RCTs were not comparable.

Detailed presentation (Tables 89 & 90).

The 7-year WHI trial that enrolled 36,282 postmenopausal women across the US compared a daily supplement of vitamin 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.⁷¹ The median serum 25(OH)D level of the study population was 42 nmol/L. The trial did not find significant effect of combined vitamin D₃ and calcium supplementation on either the risk of total cancer (adjusted HR: 0.98, 95 percent CI 0.91, 1.05) or total cancer mortality (adjusted HR: 0.89, 95 percent CI 0.77, 1.03). The methodological quality of this study was rated B.

A 4-year population based RCT,⁵² sampled from a 9-county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin 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 percent 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 percent CI 0.09, 0.60; P= 0.005). The methodological quality of this study was rated B.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** No data
- **51 – 70 y** No data
- **≥71 y** No data

- **Postmenopause** The WHI trial using vitamin 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 89. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|---|---|---|---|-----------------|
| Wactawski-Wende 2006 ⁷¹ WHI US (various) [16481636] | <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 page 242 |
| Lappe 2007 ⁵² 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 |

Table 90. Combined vitamin D and calcium and total cancer incidence: Results of RCTs

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Followup, year | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|--|------------------------------|---|-------|-------------------|---|------------|------------|--------------------------------------|--------|-------------|--------|------------------|
| Wactawski-Wende 2006 ⁷¹ WHI [16481636] | Post- menopausal women | Incident cancer (all causes) | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 1634 | 18176 | Adjusted HR (Vit D+Ca)/placebo | 0.98 | 0.91, 1.05 | 0.53 | B |
| | | | | | Placebo | 1655 | 18106 | | | | | |
| | Post- menopausal women | Total cancer mortality | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 344 | 18176 | Adjusted HR (Vit D+Ca)/placebo | 0.89 | 0.77, 1.03 | 0.12 | |
| | | | | | Placebo | 382 | 18106 | | | | | |
| Lappe 2007 ⁵² [17556697] | Post- menopausal women | Incident cancer (all causes) | 2° | 4 | Vit D ₃ 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg) | 13 | 446 | RR (Vit D+Ca)/placebo | 0.40 | 0.20, -0.82 | 0.01 | B |
| | | | | | Placebo | 20 | 288 | | | | | |
| | Post- menopausal women | Incident cancer (restrict to subjects who were free of cancer at 1 y intervention) | 2° | 4 | Vit D ₃ 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg) | 8 | 403 | RR (Vit D+Ca)/placebo | 0.23 | 0.09, -0.60 | <0.005 | |
| | | | | | Placebo | 20 | 288 | | | | | |

Colorectal cancer.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and colorectal cancer mortality or incidence. One B quality RCT of postmenopausal women reported no significant association between supplemental vitamin D₃ and calcium and, colorectal cancer mortality or incidence.

Detailed presentation (Table 91 & 92).

The WHI 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.⁷¹ 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 calcium or vitamin D supplements; they had mean daily total calcium intake of 1151 mg and vitamin D intake of 367 IU at enrollment.

Findings per special populations.

The WHI performed 18 subgroup analyses based on baseline participant characteristics including ethnic groups, body mass index, smoking status, and geographic regions according to solar irradiance.⁷¹ No significant interactions were found with these baseline characteristics. The same RCT with multifactorial design reported an interaction between estrogen alone or combined estrogen and progestin therapy, and combined vitamin D and calcium supplementation for colorectal cancer risk in a post hoc analysis.²⁰³ Among women concurrently assigned to hormone replacement therapies, colorectal cancer incidence was increased in the combined supplemental vitamin D and calcium arm compared to placebo (HR 1.50, 95 percent CI 0.96, 2.33), whereas among those concurrently assigned to placebo in the estrogen trials, colorectal cancer risk was reduced in the vitamin D plus calcium arm compared to placebo (HR 0.71, 95 percent CI 0.46, 1.09) (P for interaction = 0.02).

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data
- **51 – 70 y** One trial that included women mostly within this life stage (WHI) found no significant association between combined vitamin 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 91. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments | |
|---|--|---|---|--|--------------|---|
| Wactawski-Wende 2006 ⁷¹ WHI US (various) [16481636] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Post-menopausal women nd (50-79) 0 | Total Ca intake (mg/d) (Mean for both groups: 1151) Ca + Vit D arm: 1148 <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 page 242 | The outcomes were based on self-reported questionnaires. Only colorectal cancers were verified centrally. Colorectal cancer screening was not mandated in the protocol. Lost to followup: <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 92. Combined vitamin D with calcium and colorectal cancer: Results of RCTs

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality | |
|--|------------------------------|-----------------------------------|-------|------------------------|--|------------|------------|--------------------------------|--------|------------|------------|------------------|--|
| Wactawski-Wende 2006 ⁷¹ WHI [16481636] | Post- menopausal women | Colorectal cancer mortality | 2° | 7 | Vit D3 400 IU + Ca carbonate 1000 mg | 34 | 18,176 | HR (Suppl/Placebo) | 0.82 | 0.52, 1.29 | 0.39 | B | |
| | | | | | Placebo | 41 | 18,106 | | | | | | |
| | | Colorectal cancer | 2° | | | Vit D + Ca | 168 | 18,176 | HR | 1.08 | 0.86, 1.34 | 0.51 | |
| | | | | | | Placebo | 154 | 18,106 | | | | | |
| | | Colon cancer | 2° | | | Vit D + Ca | 128 | 18,176 | HR | 1.00 | 0.78, 1.28 | 0.99 | |
| | | | | | | Placebo | 126 | 18,106 | | | | | |
| | | Rectal cancer | 2° | | | Vit D + Ca | 44 | 18,176 | HR | 1.46 | 0.92, 2.32 | 0.11 | |
| | | | | | | Placebo | 30 | 18,106 | | | | | |

Colorectal adenoma. Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and incidence of intestinal adenoma. One B quality RCT of postmenopausal women found no significant effect of combined vitamin 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 (Table 91 & 92).

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.⁷¹ At 7 years, the incidence of adenoma was not significantly different between the supplement and placebo groups (p=0.71). All the adenoma cases were based on self-reported data, not verified by medical record review or histopathology report.

A post hoc subgroup analysis of the CPP trial of secondary adenoma prevention on the basis of calcium supplementation (1200 mg of elemental calcium) evaluated the risk of colorectal adenoma stratified by baseline 25(OH)D concentrations.²⁰⁴ The primary endpoint of the original trial was the risk of recurrent adenoma. After 4 years, in the subgroup with 25(OH)D concentrations greater than 72.6 nmol/L at baseline, subjects who received supplemental calcium had a significantly lower incidence of recurrent adenoma compared to placebo (HR=0.71 [95 percent CI 0.57,0.89] versus HR=1.05 [95 percent CI 0.85, 1.29]; interaction P=0.01). In the subgroup with 25(OH)D concentrations lower than 72.6 nmol/L, the risk of recurrence was not significantly different between supplemental calcium and placebo. No subgroup data were available regarding sex, separate life stages, or other special populations (e.g., obese, smokers, ethnic groups, or users of contraceptives).

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **51 – 70 y** The analysis of the CPP with a mean age of 61 years included participants mostly within this life stage. The study found a significant association between supplemental calcium and reduced risk of colorectal adenoma in a subgroup with 25(OH)D concentrations higher than 72.6 nmol/L.
- **71+** The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **Postmenopause** The WHI found no association between combined vitamin 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 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 without a prior history of breast cancer.²⁰⁵ No statistically significant effect was found with combined vitamin D and calcium supplementation on incident breast cancer outcome. No significant associations were found for breast cancer related mortality.

Detailed presentation (Tables 93 & 94)

In the WHI trial, the evaluated breast cancer incidence and breast cancer related mortality outcomes were secondary outcomes.²⁰⁵ There were no significant effects of combined vitamin D and calcium supplementation on both outcomes. The authors concluded that invasive breast cancer incidence was similar in the two groups of healthy postmenopausal women: calcium and vitamin D supplementation and placebo groups. The relationship of 25(OH)D serum concentrations and the risk of breast cancer was examined in a nested case-control design. The study found no relationship between total vitamin D intake and 25(OH)D serum concentrations with the risk of breast cancer.

Findings per intake level

No conclusions are possible regarding a dose effect from this single study, especially since the women in the intervention and placebo groups were allowed to take additional concurrent calcium and vitamin D supplements.

Findings by age and sex

The study investigated postmenopausal women 50 to 79 years old.

Findings by life stage

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data available
- **51 – 70 y** The WHI trial that included women mostly within this life stage found no significant effect of combined vitamin 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 93. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments | |
|--|--|--|---|--|--------------|---|
| Chebowski 2008 ²⁰⁵ WHI US (various) [19001601] | <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 94. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|---|-------------------|--|-------------------------|---------------------|---|------------|------------|--------------------------------|--------|------------|----------|------------------|
| Chebowski 2008 ²⁰⁵ WHI [19001601] | 50-79 y, Women | Breast cancer incidence | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 668 | 18176 | HR (Suppl/Placebo) | 0.96 | 0.86, 1.07 | NS | B |
| | | | | | Placebo | 693 | 18106 | | | | | |
| | | Death from breast cancer | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 23 | 18176 | HR | 0.99 | 0.55, 1.76 | NS | |
| | | | | | Placebo | 23 | 18106 | | | | | |
| | | Invasive breast cancer – subgroup >67.6 baseline 25(OH)D | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 86 | 195 | Adj OR | 0.89 | 0.58, 1.36 | NS | |
| | | | | | Placebo | 76 | 185 | | | | | |
| | | Invasive breast cancer – subgroup 55.4-<67.6 baseline 25(OH)D | 2° | 7 | Vit D ₃ + Ca | 95 | 171 | Adj OR | 1.25 | 0.83, 1.90 | NS | |
| | | | | | Placebo | 86 | 171 | | | | | |
| | | Invasive breast cancer – subgroup 43.9- <55.4 baseline 25(OH)D | 2° | 7 | Vit D ₃ + Ca | 102 | 176 | Adj OR | 1.07 | 0.70, 1.62 | NS | |
| | | | | | Placebo | 92 | 195 | | | | | |
| Invasive breast cancer – subgroup 32.4-<43.9 baseline 25(OH)D | 2° | 7 | Vit D ₃ + Ca | 71 | 185 | Adj OR | 0.69 | 0.45, 1.06 | NS | | | |
| | | | Placebo | 102 | 171 | | | | | | | |
| Invasive breast cancer – subgroup <32.4 baseline 25(OH)D | 2° | 7 | Vit D ₃ + Ca | 94 | 171 | Adj OR | 0.91 | 0.60, 1.39 | NS | | | |
| | | | Placebo | 91 | 176 | | | | | | | |

Combined Vitamin D and Calcium and Pregnancy-related Outcomes

Preeclampsia.

Synopsis.

Based on data from a single RCT, there is no significant effect of combined vitamin D and calcium supplementation on the prevention of preeclampsia.

Detailed presentation (Tables 95 & 96.)

One RCT from India used a combination of vitamin D (1200 IU/d) and calcium (375 mg/d) for the prevention of preeclampsia.²⁰⁶ **Table 85** describes the characteristics of the trial. The trial found no significant difference between the compared arms (**Table 86**). Note that this RCT was excluded from the meta-analysis of trials for preeclampsia in the calcium section.

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** Not applicable
- **3 – 8 y** Not applicable
- **9 – 18 y** Not applicable
- **19 – 50 y** [see pregnant and lactating women]
- **51 – 70 y** Not applicable
- **71+** Not applicable
- **Postmenopause** Not applicable
- **Pregnant & lactating women** Based on data from a single RCT, there is no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) supplementation on the prevention of preeclampsia.

Other pregnancy-related outcomes.

Synopsis.

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

Table 95. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|---|---|--|--|----------|
| Marya 1987 ²⁰⁶ India (29°N) [3623260] | <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 96. Combined vitamin D and calcium and preeclampsia: Results of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Compari- son) | Result | 95% CI | P Btw | Study Quality |
|---|------------|---------------------------|-------|------------------------|---------------------------------------|------------|------------|---|--------|------------|----------|------------------|
| Marya 1987 ²⁰⁶ India (29°N) [3623260] | Pregnancy | Toxemia (preeclampsia) | 1° | ND | Vit D (1200 IU) & calcium (375 mg) | 12 | 200 | RR (combined Vit D & Ca vs. nothing) | 0.67 | 0.33, 1.35 | 0.26 | C |
| | | | | | No supplement | 18 | 200 | | | | | |

Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health

Rickets, fractures, falls, or performance measures.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34**).⁶ Because the Ottawa's EPC report did not have separate analyses for the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation are presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. Only RCTs qualified for inclusion.

Synopsis.

The Ottawa EPC report concluded that supplementation with vitamin D (most studies used 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 analyzed the performance measure outcomes in a small sample of postmenopausal women from WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo groups after 5 years of followup.²⁰⁷ One RCT of premenopausal women, aged 17 to 35 years old, showed that 800 IU/d of vitamin D in combination with 2000 mg/d of calcium supplementation can reduce the risk of stress fracture from military training compared to placebo.²⁰⁸

Detailed presentation (Table 34, 97, 98 & 99).

One RCT of female Navy recruits, aged 17 to 35 years, aimed to determine whether supplementation with vitamin D (800 IU/d) plus calcium (2000 mg/d) can reduce the risk of stress fractures from military training near the Great Lakes (41°N).²⁰⁸ The median dairy intake was <1 serving/day, which provided less than 300 mg of calcium. The combined supplementation significantly reduced the risk of stress fractures by 20 percent compared to placebo. The methodological quality of this study was rated B.

One study analyzed the performance measure outcomes in a sample of 2928 postmenopausal women from the WHI trial who had objective physical function measures.²⁰⁷ The results showed that physical function, measured by grip strength, chair stands, and walking time, had generally declined in postmenopausal women who were assigned to either vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo group. However, women who had received vitamin D plus calcium supplementation showed less declines in walking time than those who had received placebo. The methodological quality of this study was rated C because only a small proportion of women from the WHI trial were in the analyses and their baseline characteristics were unclear.

From the Ottawa EPC Report: Fractures - Postmenopausal women and older men.

Fifteen RCTs examined the effect of either vitamin 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 percent CI 0.80, 0.99). The individual treatment effects ranged from OR 0.28 (95 percent CI 0.12, 0.67) to 1.16 (95 percent CI 0.70, 1.92). In the two cluster RCTs, one demonstrated a significant reduction in the risk of falls in postmenopausal women taking vitamin D₃ plus calcium (RR 0.88, 95 percent CI 0.79, 0.98), whereas the other trial did not show a significant reduction in the risk of falls in elderly individuals taking vitamin D₂ (RR 1.09, 95 percent 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 followup did not.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** The Ottawa EPC report concluded that supplementation with vitamin D (most studies used 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** No new data since the Ottawa report
- **71+** No new data since the Ottawa report

- **Postmenopause** One study analyzed the performance measure outcomes in a small sample of postmenopausal women from the WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation and placebo groups after 5 years of followup.
- **Pregnant & lactating women** No data

Table 97. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|--|--|--|---|--|
| Lappe 2008 ²⁰⁸ Great Lakes, IL, US (41°N) [18433305] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | Assumed healthy (Navy recruits) 19 (17-35) 0 | Mean dairy servings/wk = 6 (ranged 1-26) | Vit D 800 IU/d + Ca 2000 mg/d vs. Placebo | Monitor pill taking: project staff observed the galley food lines, visited recruits in their quarters, and conducted an exit interview. |
| Brunner 2008 ²⁰⁷ WHI US (various) [18755319] | <ul style="list-style-type: none"> • Health status • Mean age (range), y • Male (%) | nd (for the sub sample from WHI trial) 50-79 0 | nd | Vit D 400 IU/d + Ca 1000 mg/d vs. Placebo | nd (however, adherence was assessed at least annually from the weight of remaining pills along with a structured interview in WHI trial) A sub sample from WHI trial. Post hoc analyses of a RCT. |

Table 98. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture)

| Author Year Study Name [PMID] | Life Stage | Outcome | 1°/2° | Mean Followup, mo | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality |
|--------------------------------------|---------------|---|-------|-------------------|---------------------------|---------|---------|--------------------------------|--------|------------|-------|---------------|
| Lappe 2008 ²⁰⁸ [18433305] | 17-35 y women | Stress fracture from Navy training (ITT) | 1° | 2 | Vit D 800 IU + Ca 200 mg | 139 | 2626 | RR (Vit D+Ca)/placebo | 0.8 | 0.64, 0.99 | 0.026 | B |
| | | | | | Placebo | 170 | 2575 | | | | | |
| | | Stress fracture from Navy training (per protocol) | 1° | 2 | Vit D 800 IU + Ca 200 mg | 126 | 1852 | Adjusted OR (Vit D+Ca)/placebo | 0.79 | 0.62, 1.01 | 0.059 | |
| | | | | | Placebo | 160 | 1848 | | | | | |

Table 99. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures)

| Author Year Study Name PMID | Life Stage | Outcome | 1°/2° | Mean Followup, mo | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change SD | Net Diff | Net Diff 95% CI | P Btw | Study Quality | |
|--|----------------|---------------|-------|-------------------|-------------------------------------|--------------|---------|----------|--------|-----------|----------|-----------------|-------|---------------|--|
| Brunner 2008 ²⁰⁷ [18755319] | Post-menopause | Grip strength | 2° | 60 | Vit D 400 IU + Ca carbonate 1000 mg | 1185 | kg | 22.81 | -2.49 | 5.81 | 0.15 | 0.24 | 0.52 | C | |
| | | | | | Placebo | 1162 | | 22.96 | -2.64 | 5.69 | | | | | |
| | | Chair stands | 2° | 60 | Vit D 400 IU + Ca carbonate 1000 mg | 1065 | counts | 6.52 | -0.38 | 1.81 | 0.04 | 0.08 | 0.603 | | |
| | | | | | Placebo | 1053 | | 6.63 | -0.43 | 1.81 | | | | | |
| | | Walking time | 2° | 60 | Vit D 400 IU + Ca carbonate 1000 mg | 1160 | seconds | | +0.26 | 6.28 | - | 0.54 | 0.26 | 0.030 | |
| | | | | | Placebo | 1141 | | | +0.81 | 6.43 | | | | | |

Combined Vitamin D and Calcium and all-cause Mortality

Synopsis.

This synopsis is based on a meta-analysis of RCTs of combined vitamin D and calcium supplementation evaluating mortality. Numerical data were extracted from previous systematic reviews. Most trials used daily regimens; in these trials, vitamin D doses ranged between 300 and 880 IU per day. Most trials combined vitamin D and calcium supplementation; when used, calcium doses ranged between 500 and 1200 mg per day.

Our meta-analysis of 11 RCTs (44,688 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.93, 95 percent CI 0.86, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses. Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity.

Although the meta-analyses suggest decreased risk for all-cause mortality with combined vitamin D and calcium supplementation, the relationship is not statistically significant in the performed analyses.

Detailed presentation (Table 37; Figure 22).

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

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

As described in the vitamin D and all-cause mortality section, we identified two potentially eligible systematic reviews,^{83,84} and selected one as the basis for our reanalysis (Autier 2007).⁸³ Table 37 in the “Vitamin D” section summarizes the findings of the Autier 2007 systematic review.

As detailed below, we identified one additional trial of combined vitamin D and calcium supplementation reporting all-cause mortality.²⁰⁹

Eligible studies published after the systematic reviews.

The literature searches in Autier 2007 extended up to November 2006. We identified two additional RCT reports published after November 2006.^{71,209} One publication⁷¹ reported on the same trial as another publication²¹⁰ in the Autier 2007 meta-analysis, and was therefore excluded from our reanalysis. The other RCT (Bjorkman 2008²⁰⁹) was included in our meta-analysis.

One three-arm RCT (Bjorkman 2008²⁰⁹, 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.

We excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,⁸⁵ one was published only in abstract form,⁸⁶ and in the last trial the controls also received supplementation with vitamin D, albeit with a smaller dose,⁸⁷ and two used injections of vitamin D.^{88,89} Altogether, 11 RCTs were included in the reanalysis of combined vitamin D and calcium supplementation and all-cause mortality (i.e., 10 out of 18 in the Autier 2007 meta-analysis, and a subsequently published one²⁰⁹).

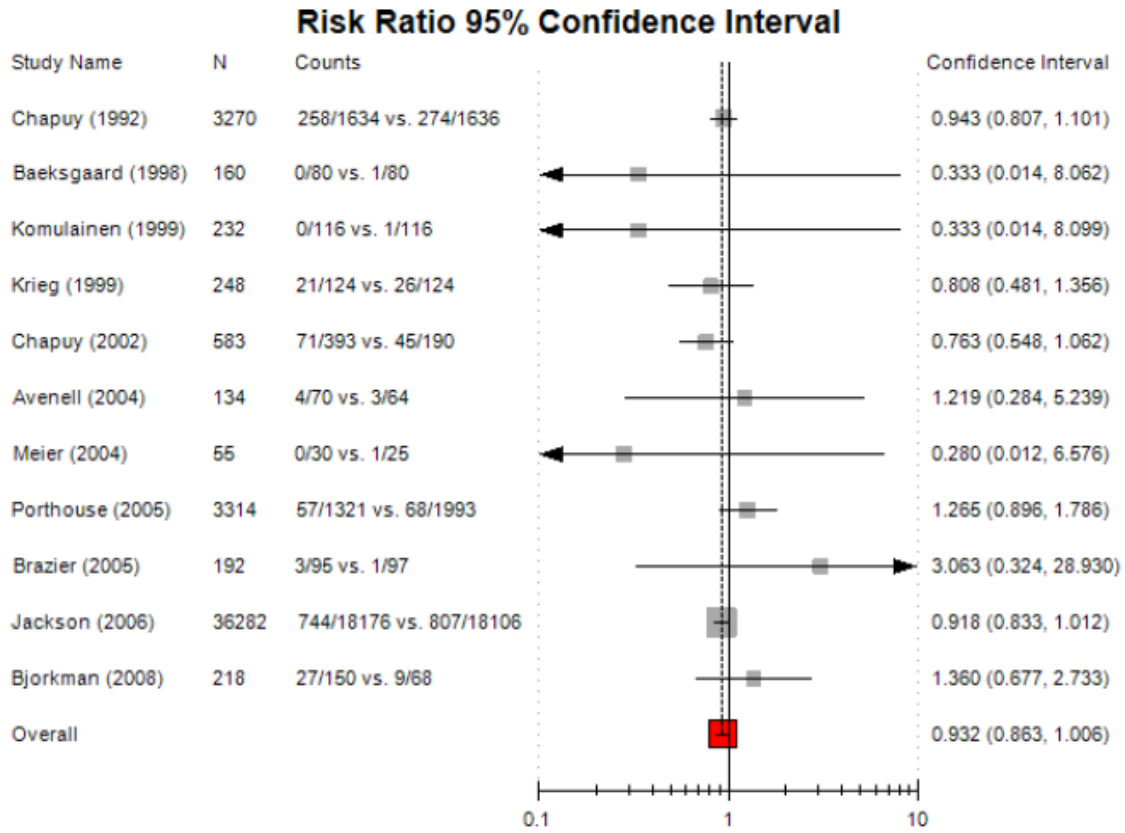
Among the 12 trials, sample sizes ranged from 55 to 36,282 participants, with 7 studies including more than 500 participants. Followup periods ranged from 6 to 84 months (median 24 months). Vitamin D doses in most trials ranged between 300 and 880 IU per day. One trial used 100,000 IU orally every 4 months. Calcium supplementation doses ranged between 500 to 1200 mg per day.

Overall, a meta-analysis of the 11 RCTs (44,688 participants; Figure 22) found no statistically significant relationship between vitamin D and all-cause mortality (RR=0.93, 95 percent CI 0.86, 1.01). There is little evidence for between-study heterogeneity in these analyses (P=0.58, I^2 =0 percent). Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity (P=0.46, I^2 =0 percent). There are no RCTs with mean participant age below 50 years. It is unclear whether these findings are directly applicable to other life stages. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95 percent CI 0.84, 1.15), with little evidence for between study heterogeneity (P=0.33, I^2 =13 percent).

Findings by life stage.

- **0 – 6 mo** No data
- **7 mo – 2 y** No data
- **3 – 8 y** No data
- **9 – 18 y** No data
- **19 – 50 y** No data
- **51 – 70 y** Our meta-analysis of 12 RCTs (44,838 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.94, 95 percent CI 0.87, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses.
- **71+** The above are likely applicable here. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95 percent CI 0.84, 1.15), with little evidence for between study heterogeneity.
- **Postmenopause** Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95 percent CI 0.86, 1.00), again with little evidence for between-study heterogeneity.
- **Pregnant & lactating women** No data

Figure 22. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality.



Combined Vitamin D and Calcium and Hypertension and Blood Pressure.

We reviewed systematic reviews and primary studies that evaluated associations between combined vitamin D and calcium intake and incidence of hypertension or change in blood pressure. For the outcome incidence of hypertension, we included RCTs and other longitudinal studies. For the outcome change in blood pressure, we included only RCTs. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the “Pregnancy-related outcomes” section.

Combined vitamin D and calcium and hypertension.

Synopsis.

No qualified systematic reviews evaluated the association between combined vitamin D and calcium intake, body stores, or serum concentrations and incidence of hypertension. The WHI trial reported an analysis of the risk of developing hypertension among the subset of women without hypertension at baseline. Over 7 years, combined vitamin D and calcium supplementation had no effect on the risk of hypertension.

Detailed presentation (Tables 100 & 101).

The WHI trial of a combined vitamin 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).²¹¹ The women were allowed to take additional concurrent calcium and vitamin D supplements. The analysis of incident hypertension was reported briefly in a larger analysis of the blood pressure outcome (see *Combined vitamin D and calcium and blood pressure*, below). Among 17,122 initially nonhypertensive women, 39 percent either were prescribed medication for hypertension or developed blood pressure above 140/90 mm Hg. The adjusted HR of developing hypertension over 7 years was 1.01 (95 percent CI 0.96, 1.06). Among 377 women with available data, there was a statistically significant trend across subgroups based on serum 25(OH)D concentration such that combined vitamin D and calcium supplementation *increased* the risk of developing hypertension more in those women with progressively *lower* baseline 25(OH)D (P<0.01 for trend). Other subgroup analyses based on age, race or ethnicity, weight, or baseline total calcium intake did not find any interactions with the effect of the supplement intervention.

Findings per intake level.

This single trial did not analyze different actual intake levels.

Findings by age and sex.

This trial found no difference in (lack of) effect by age among postmenopausal women.

Findings by life stage.

- **0 – 6 mo** Not reviewed
- **7 mo – 2 y** Not reviewed
- **3 – 8 y** Not reviewed
- **9 – 18 y** Not reviewed
- **19 – 50 y** No data.

- **51 – 70 y** One large trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **≥71 y** The WHI trial included some women within the life stage, but no study adequately evaluated this life stage.
- **Postmenopause** All women in the WHI trial were postmenopausal. See 51-71 y life stage.
- **Pregnant & lactating women** Not reviewed

Table 100. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|--|--|--|---|
| Margolis 2008 ²¹¹ WHI US (various) [18824662] | <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 101. Combined vitamin D and calcium and incident hypertension: Results of RCTs

| Author Year Study Name [PMID] | Life Stage [Subgp] | Outcome | 1°/2° | Mean Followup, y | Interventions, Daily Dose | n Event | N Total | Outcome Metric (Comparison) | Result | 95% CI | P Btw | Study Quality | |
|--|-----------------------|---------|-------|---------------------|---|------------|------------|--------------------------------|--------|------------|------------|------------------|----|
| Margolis 2008 ²¹¹ WHI [18824662] | 50-79 y, Women | HTN | 2° | 7 | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 3377 | ~8578 | HR (Suppl/Placebo) | 1.01 | 0.96, 1.06 | 0.69 | B | |
| | | | | | Placebo | 3315 | ~8544 | | | | | | |
| | | | | | [25(OH)D <34.4 nmol/L] | Vit D + Ca | 53 | | | 1.52 | 0.89, 2.59 | | NS |
| | | | | | | Placebo | 38 | | | | | | |
| | | | | | [25(OH)D 34.4-47.6 nmol/L] | Vit D + Ca | 39 | | | 1.48 | 0.89, 2.46 | | NS |
| | | | | | | Placebo | 48 | | | | | | |
| | | | | | [25(OH)D 47.7-64.6 nmol/L] | Vit D + Ca | 45 | | | 1.15 | 0.69, 1.92 | | NS |
| | | | | | | Placebo | 45 | | | | | | |
| | | | | | [25(OH)D ≥64.7 nmol/L] | Vit D + Ca | 48 | | | 0.79 | 0.51, 1.22 | | NS |
| | Placebo | 61 | | | | | | | | | | | |

Combined vitamin D and calcium and blood pressure.

Synopsis.

No qualified systematic reviews evaluated the association between vitamin D and calcium intake, body stores, or serum concentrations, and changes in blood pressure. Two RCTs compared combined vitamin D and calcium supplementation with placebo. Both the small trial of a combined vitamin 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 102 & 103).

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).²¹¹ On average, the women had normal blood pressure and were allowed to take additional concurrent calcium and vitamin D supplements. At 74 months, the women's mean systolic blood pressure had risen and diastolic blood pressure had fallen in both trial arms (by less than about 2 mm Hg each at 2 years¹⁹⁹). The absolute changes were not significantly different in the women assigned to the supplement than placebo (net difference 0.2 mm Hg systolic and 0.1 mm Hg diastolic). In subgroup analyses there was no differences in results by age, ethnicity, baseline total calcium intake, baseline diagnosis of hypertension, or a variety of other factors.

The C quality trial of combined vitamin D and calcium, performed in Quebec City, recruited premenopausal women (mean age 43 y) with low calcium intake (800 mg calcium per day) who did not have severe hypertension (blood pressure over 160/95 mm Hg).²⁰² The mean baseline calcium intake was 704 mg/day. On average, the 63 women had normal blood pressure. They were given either combined vitamin 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 102. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs

| Author Year Study Name Location (Latitude) [PMID] | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|--|---|--|--|--|
| Margolis 2008 ²¹¹ WHI US (various) [18824662] | <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 ≥1200 mg/d | Combined Vit D + Ca supplement vs. Placebo | See page 242 Mean dose of open label supplemental Ca increased by <100 mg/d from 325 mg/d at enrollment; similar in both groups |
| Major 2007 ²⁰² Quebec City, Canada (47°N) [17209177] | <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 103. Combined vitamin D and calcium and blood pressure: Results of RCTs

| Author Year Study Name [PMID] | Age Range, Sex | Outcome | 1°/2° | Mean Followup | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|---|----------------------|---------|-------|------------------|--|-----------------|----------|------------------|--------------------|------------------|-------------|--------------------|----------|------------------|
| SYSTOLIC BLOOD PRESSURE | | | | | | | | | | | | | | |
| Margolis 2008 ²¹¹ WHI [18824662] | 50-79, Women | SBP | 2° | 6.1 y | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 18,176 | mm Hg | 127 ^A | +1.1% ^A | 0.9, 1.3 | +0.22 | -0.05, +0.49 | 0.11 | B |
| | | | | | Placebo | 18,106 | | 128 ^A | +0.7% ^A | 0.5, 0.9 | | | | |
| Major 2007 ²⁰² Quebec City [17209177] | 43 (5.5), Women | SBP | 2° | 15 wk | Vit D ₃ 400 IU + Ca carbonate 1200 mg (energy restriction diet) | 30 | mm Hg | 112.4 | -4.1 | -6.5, -1.7 | -2.5 | -6.2, 1.2* | 0.18 | C |
| | | | | | Placebo (energy restriction diet) | 33 | | 109.5 | -1.6 | -4.2, 1.0 | | | | |
| DIASTOLIC BLOOD PRESSURE | | | | | | | | | | | | | | |
| Margolis 2008 ²¹¹ WHI [18824662] | 50-79, Women | DBP | 2° | 6.1 y | Vit D ₃ 400 IU + Ca carbonate 1000 mg | 18,176 | mm Hg | 76 ^A | -0.2% ^A | -0.4, - 0.02 | +0.11 | -0.04, +0.27 | 0.14 | B |
| | | | | | Placebo | 18,106 | | 76 ^A | -0.6% ^A | -0.8, -0.4 | | | | |
| Major 2007 ²⁰² Quebec City [17209177] | 43 (5.5), Women | DBP | 2° | 15 wk | Vit D ₃ 400 IU + Ca carbonate 1200 mg (energy restriction diet) | 30 | mm Hg | 74.9 | -3.0 | -4.8, -1.2 | 0 | -2.7, 2.7* | 1.0 | C |
| | | | | | Placebo (energy restriction diet) | 33 | | 75.2 | -3.0 | -5.0, -1.0 | | | | |

^A Hsia 2007¹⁹⁹ [17309935]

Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34**).⁶ Because the Ottawa's EPC report did not have separate analyses on the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation were presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. For adults, we included only BMD indices. For children, we included only BMC indices. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

One RCT found that, compared to placebo, there was no significant effect of supplementation with vitamin 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.⁶ 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 (Table 34, 104 & 105).

One RCT 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.²¹² The mean background dietary calcium intake was 670 mg/d. The intention-to-treat analyses showed that after 2 years of supplementation, there was no significant difference in the BMC changes between girls who received vitamin D plus calcium supplement or placebo. The methodological quality of this study was rated C, due to underpower and low compliance rate.

Three RCTs (two were rated B and one was rated C) examined the effect of vitamin D plus calcium supplementation on BMD changes. All three trials were conducted in postmenopausal women. However, the doses of vitamin D and calcium combinations varied. One RCT used daily dose of 400 IU vitamin D₃ plus 100 mg elemental calcium for 2 years.²¹³ The second RCT used daily dose of 1000 IU vitamin D₂ plus 1200 mg calcium citrate for 5 years.²¹⁴ 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.²¹⁵ The latter two RCTs resulted in a significant increase in hip or total BMD comparing vitamin D plus calcium supplementation to placebo.^{214,215} The one RCT that did not show significant change in femoral neck BMD comparing vitamin D plus calcium supplementation to placebo used a substantially lower dose of calcium (100 mg/d) than the other two RCTs.

In Ottawa EPC report - Bone Mineral Density and women of reproductive age, postmenopausal women, and older men.

Overall, there is good evidence that vitamin 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 104. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report

| Author Year Study Name Location (Latitude) [PMID] | | Population | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|--|--|--|--|---|--|--|
| Cheng 2005 ²¹² Jyvaskyla, Finland (62°24'N) [16280447] | <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 ²¹³ (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 ²¹⁴ 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 ²¹⁵ 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 |

Table 105. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report

| Author Year Study Name PMID | Life Stage | Outcome | 1°/2° | Mean Followup, mo | Interventions, Daily Dose | No. Analyzed | Unit | Baseline | Change | Change 95% CI | Net Diff | Net Diff 95% CI | P Btw | Study Quality |
|---|-------------------------|------------------------|-------|-------------------------|--|--------------------|--------------------|----------|--------|------------------|-------------|--------------------------|----------|------------------|
| Cheng 2005 ²¹² [16280447] | 10-12 y girls | BMC | 1° | 24 | Vit D 200 IU + Ca carbonate 1000 mg | 46 | kg | 1.3 | 34.7% | 34.3%, 35.1% | -0.3% | -0.8, 0.2 ^A | NS | C |
| | | | | | Placebo | 39 | | 1.3 | 35.0% | 34.6%, 35.4% | | | | |
| Bolton-Smith 2007 ²¹³ [17243866] | Postmenopausal women | Femoral neck BMD | nd | 24 | Vit D ₃ 400 IU + Elemental Ca 100 mg | 50 | mg/cm ² | nd | +1.9 | -6.5, 10.3 | +1.2 | -12.6, 15.0 ^A | NS | B |
| | | | | | Placebo | 56 | | nd | +0.7 | -10.2, 11.6 | | | | |
| Zhu 2008 ²¹⁴ Australia CIFOS [18089701] | Postmenopausal women | Hip BMD | 1° | 60 | Vit D ₂ 1000 IU + Ca citrate 1200 mg | 39/33 ^B | mg/cm ² | 783 | nd | | +2.2% | 1.9, 2.5 | 0.05 | B |
| | | | | | Placebo | 41/36 ^B | | 828 | nd | | | | | |
| Moschonis 2006 ²¹⁵ [17181890] | Postmenopausal women | Total body BMD | 1° | 12 | Vit D ₃ 300 IU + Ca 1200 mg (from low fat dairy products) | 39 | mg/cm ² | 1.13 | 1.5% | 0.9%, 2.2% | +2.2% | 1.3, 3.1 ^A | <0.05 | C |
| | | | | | Control (usual diet) | 36 | | 1.12 | -0.7% | -1.4%, -0.1% | | | | |

^A Estimated from reported data.

^B Baseline/follow-up number of subjects analyzed

How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D concentrations (arrow 4)?

The evidence for this question comes from studies identified in our literature search that crossed vitamin D terms with various outcomes terms. Studies that addressed this question but do not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all vitamin D supplements full text articles (in excess of 10,000) to look for serum 25(OH)D concentration data. Given that there is no plausible reason for a systematic bias of studies of a specific outcome choosing to report serum 25(OH)D concentration, we believe that the evidence found, while not comprehensive, is a small but representative random sample. Only RCTs were included for this question. RCTs of different regimens but with the same dose of vitamin D supplementation were excluded (e.g., comparison of daily, weekly versus monthly dose).

This question was also addressed in the Ottawa EPC report.⁶ When appropriate, we extracted relevant data from the Ottawa EPC report to be incorporated into our analyses.

RCTs on Dietary Intakes of Vitamin D From Fortified Foods and Serum 25(OH)D Concentrations.

Synopsis.

Our updated search did not identify new RCT evaluating the effect of food fortification on serum 25(OH)D concentrations since the Ottawa EPC report.⁶ The Ottawa EPC report concluded that there is “good” evidence that dietary intake of vitamin D increases serum 25(OH)D concentrations among adults.

Detailed presentation.

Ottawa EPC report –Adults.

There were eleven RCTs (n=1281) of which seven (n=668) permitted a quantitative analysis. Ten of eleven trials found a significant effect of dietary intake from foods fortified with vitamin D on serum 25(OH)D concentrations. There was significant heterogeneity of the treatment effect. Potential sources of heterogeneity are the different 25(OH)D assays used (two studies each used HPLC, RIA or CPBA, and one study did not report the assay), the dietary vehicles used, and study populations. The increase in serum vitamin D concentration in the seven trials ranged from 15 (95 percent CI 11, 18) to 40 (95 percent CI 25, 55) nmol/L (fortification consisting of 100 - 1000 IU of vitamin D).

There can be a potential confounding of the data by the food source, the assay used to measure 25(OH)D and potential differences in the bioavailability and/or metabolism of vitamin 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.

RCTs on Vitamin D Supplementation and Serum 25(OH)D Concentrations.

Synopsis.

Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. We believe that studies summarized here is a small but representative random sample of all available data.

We plot the net changes in serum 25(OH)D concentration against the doses of vitamin D supplementation using data from 26 RCTs with 28 comparisons in adults. Only RCTs of daily vitamin 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 23). 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 24), and depending on duration of supplementation (≤ 3 vs. >3 months) (Figure 25).

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 106; Figures 23, 24 & 25).

The results from 26 RCTs with 28 comparisons in adults and two RCTs with three comparisons in children evaluating the effect of vitamin D₃ supplementation alone or in combination with calcium supplementation on serum 25(OH)D concentrations were shown in Table 106. Most of the data were extracted directly from the Ottawa EPC report. In adults, the doses of vitamin D₃ ranged from 200 to 5000 IU/d, and the doses of calcium supplementation ranged from 500 to 1550 mg/d across the 25 comparisons. In children, the doses of vitamin D₃ ranged from 200 to 2000 IU/d across the three comparisons. Duration of supplementation ranged from 0.5 to 60 months. Study populations and baseline vitamin D concentrations varied across these comparisons.

Ottawa EPC report – Infants.

Seven RCTs included infants and few trials used vitamin 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).

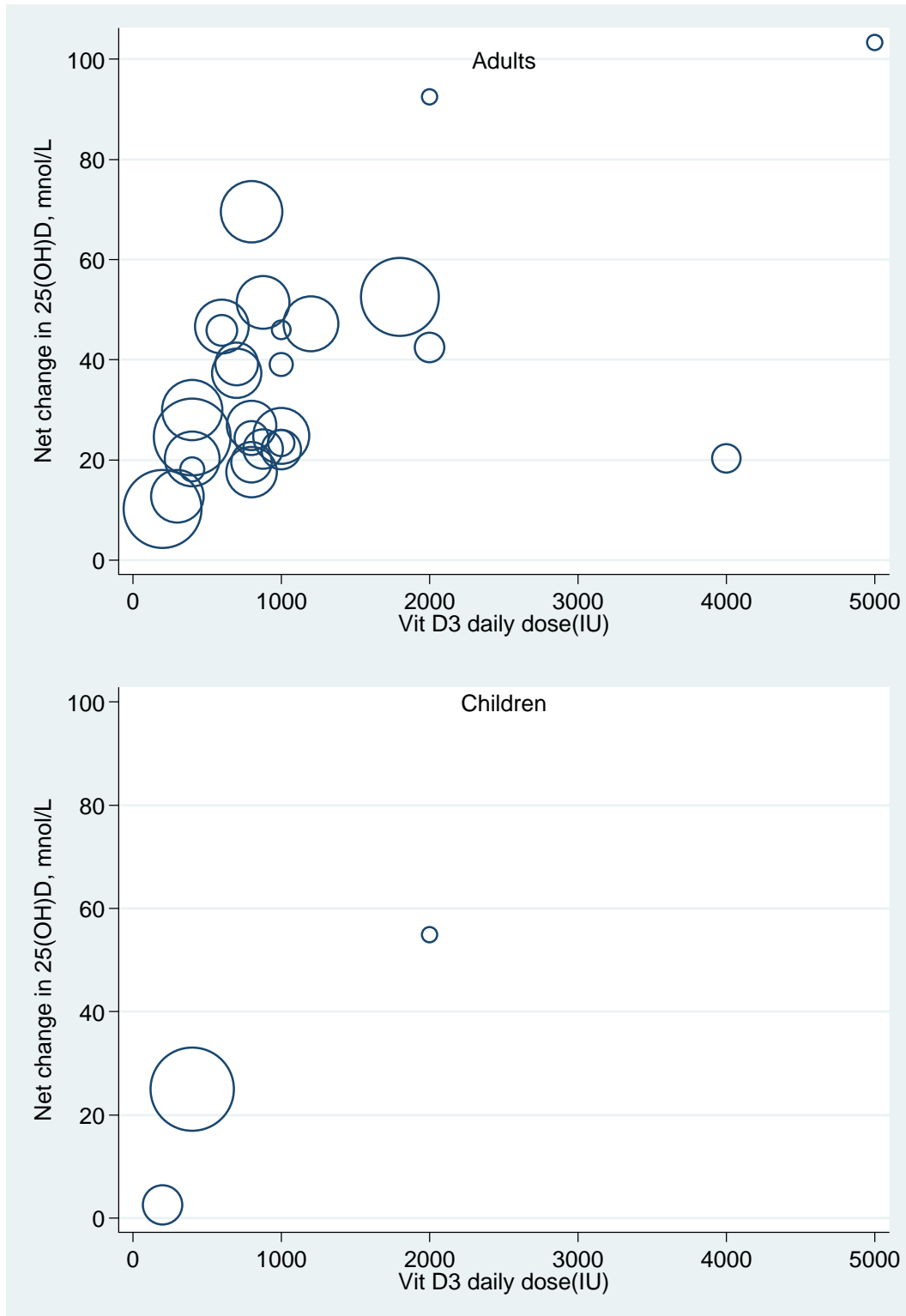
Three trials found that supplementation with vitamin D₂ and D₃ in healthy adults may have different effects on serum 25(OH)D concentrations. One trial compared 100,000 IU vitamin D₂ given orally versus injection and found a greater variability in response with the intramuscular preparation. There appeared 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.

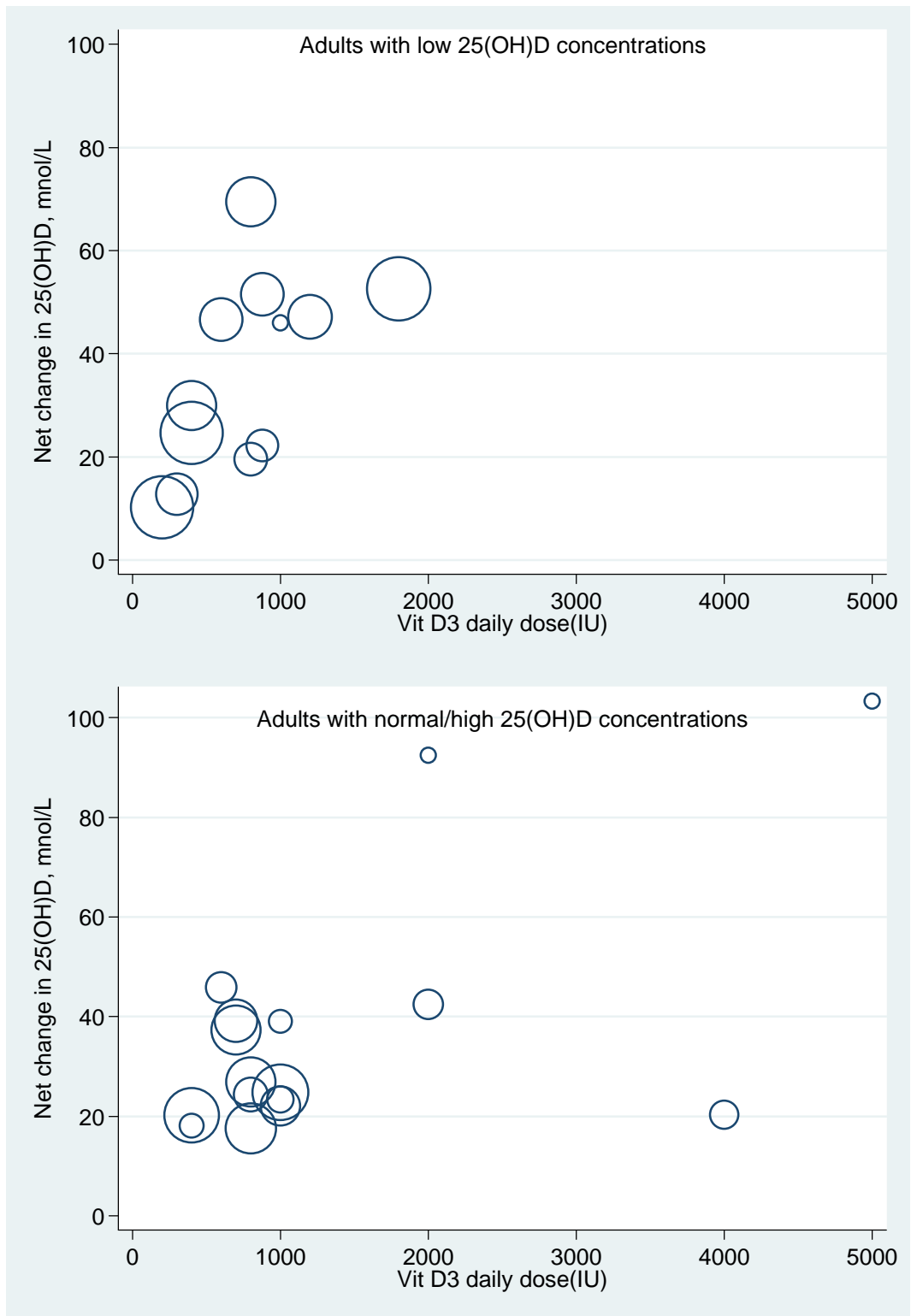
One trial found that wintertime declines in serum 25(OH)D concentrations were prevented with 500 IU vitamin D₃ per day. A dose response with increasing doses of vitamin D₃ was noted for serum 25(OH)D concentrations. There was variability in response to similar doses across trials that may have been due 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 23. Relationship between doses of Vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs



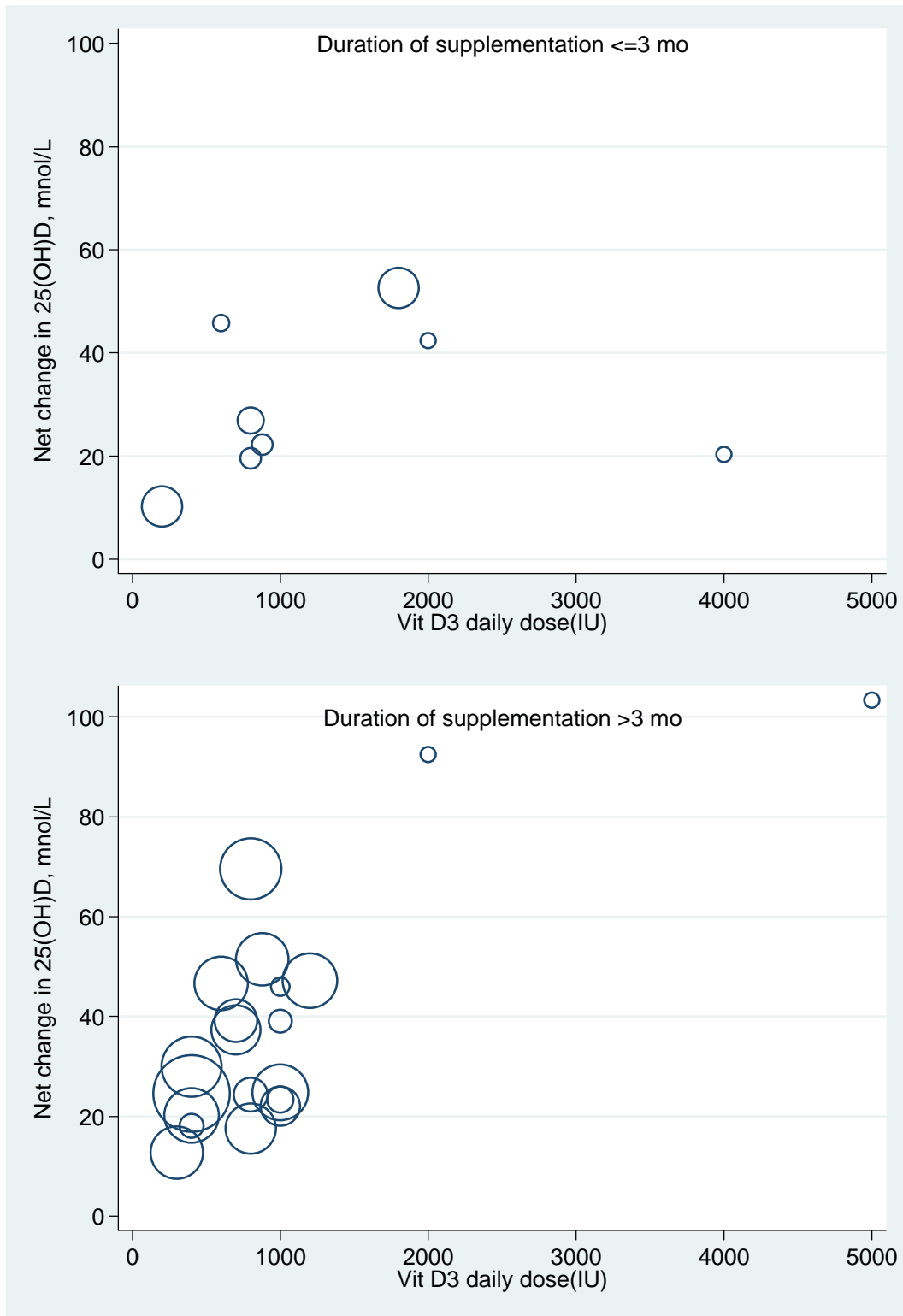
Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Figure 24. Relationship between doses of Vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults



Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Figure 25. Relationship between doses of Vitamin D₃ supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults



Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Table 106. The relationship between vitamin D₃ daily doses and changes in 25(OH)D concentrations in RCTs

| Author | Year | Life stage | Base 25(OH)D, nmol/L | Vit D ₃ dose (IU/d) | Ca dose (mg/d) | Duration (mo) | Vit D ₃ ± Ca Group | | | Placebo or Ca Group | | |
|---------------|---------------------|------------|-------------------------|-----------------------------------|-------------------|------------------|-------------------------------|------------------------------------|------|---------------------|------------------------------------|------|
| | | | | | | | n | Mean change from baseline | SD | n | Mean change from baseline | SD |
| Bjorkman | 2008 ²⁰⁹ | 71+ | 23 | 400 | 0 | 6 | 60 | 26.5 | 11.8 | 59 | 1.9 | 10.2 |
| Bjorkman | 2008 ²⁰⁹ | 71+ | 23 | 1200 | 0 | 6 | 63 | 49.1 | 19.5 | 59 | 1.9 | 10.2 |
| Blum | 2008 ²¹⁶ | 71+ | 73 | 700 | 500 ^A | 12 | 132 | 48.5 | 35.3 | 125 | 9.3 | 21.5 |
| Bunout | 2006 ⁸⁰ | 71+ | 40 | 400 | 800 ^A | 9 | 46 | 33.4 | 14.3 | 46 | 3.5 | 10.0 |
| Chapuy | 1992 ²¹⁷ | 71+ | 36 | 800 | 1200 | 18 | 73 | 65.0 | 16.5 | 69 | -4.5 | 13.5 |
| Chel | 2008 ²¹⁸ | 71+ | 23 | 600 | 0 | 4 | 46 | 46.9 | 15.4 | 45 | 0.3 | 12.2 |
| Deroisy | 2002 ²¹⁹ | 71+ | 28 | 200 | 500 ^A | 3 | 50 | 14.7 | 10.0 | 50 | 4.5 | 10.0 |
| Himmelstein | 1990 ²²⁰ | 71+ | 45 | 2000 | 0 | 1.5 | 15 | 39.7 | 15.7 | 15 | -2.7 | 13.4 |
| Kenny | 2003 ²²¹ | 71+ | 62 | 1000 | 500 ^A | 6 | 29 | 22.3 | 10.1 | 31 | -2.5 | 11.4 |
| Krieg | 1999 ²²² | 71+ | 29 | 880 | 500 | 24 | 34 | 36.5 | 14.0 | 38 | -15.0 | 11.1 |
| Pfeifer | 2000 ²²³ | 71+ | 25 | 880 | 1200 ^A | 2 | 74 | 40.5 | 27.0 | 74 | 18.3 | 20.9 |
| Pfeifer | 2001 ⁹⁷ | 71+ | 25 | 800 | 1200 | 2 | 73 | 39.2 | 22.4 | 72 | 19.7 | 23.8 |
| Sorva | 1991 ²²⁴ | 71+ | 11 | 1000 | 1000 | 10 | 5 | 44.6 | 28.9 | 10 | -1.4 | 2.3 |
| Zhu | 2008 ²¹⁴ | 71+ | 68 | 1000 | 1200 ^A | 60 | 29 | 36.2 | 27.5 | 34 | -2.9 | 27.4 |
| Barnes | 2006 ²²⁵ | adults | 52 | 600 | 1500 ^A | 2 | 12 | 38.6 | 15.1 | 15 | -7.2 | 11.3 |
| Bolton-Smith | 2007 ²¹³ | adults | 60 | 400 | 100 | 24 | 50 | 12.0 | 15.1 | 56 | -8.2 | 14.3 |
| Dawson-Hughes | 1997 ²²⁶ | adults | 74 | 700 | 500 | 36 | 145 | 35.2 | 32.6 | 167 | -2.1 | 22.7 |
| Harris | 2002 ²²⁷ | adults | 55 | 800 | 0 | 2 | 27 | 22.3 | 14.0 | 23 | -4.6 | 6.3 |
| Heaney | 2003 ²²⁸ | adults | 71 | 1000 | 0 | 5 | 16 | 12.0 | 16.0 | 16 | -11.4 | 17.6 |
| Heaney | 2003 ²²⁸ | adults | 71 | 5000 | 0 | 5 | 17 | 91.9 | 37.6 | 16 | -11.4 | 17.6 |
| Heikkinen | 1998 ²²⁹ | adults | 26 | 300 | 500 ^A | 12 | 18 | 9.4 | 10.9 | 18 | -3.3 | 6.4 |
| Honkanen | 1990 ²³⁰ | adults | 31 | 1800 | 1550 | 2.75 | 55 | 39.5 | 12.1 | 60 | -13.1 | 9.2 |
| Jensen | 2002 ²³¹ | adults | 41 | 400 | 1450 | 36 | 33 | 34.6 | 23.2 | 33 | 16.5 | 28.2 |
| Nelson | 2009 ²³² | adults | 62 | 800 | 0 | 12 | 55 | 35.3 | 23.2 | 31 | 10.9 | 16.9 |
| Orwoll | 1988 ²³³ | adults | 58 | 1000 | 1000 | 12 | 46 | 25.0 | 19.1 | 46 | 3.0 | 19.1 |
| Patel | 2001 ²³⁴ | adults | 72 | 800 | 0 | 12 | 35 | 8.4 | 13.1 | 35 | -9.2 | 12.8 |
| Riis | 1984 ²³⁵ | adults | 41 | 2000 | 500 | 12 | 8 | 87.5 | 14.1 | 7 | -5.0 | 23.8 |

continued

| Author | Year | Life stage | Base 25(OH)D, nmol/L | Vit D ₃ dose (IU/d) | Ca dose (mg/d) | Duration (mo) | Vit D ₃ ± Ca Group | | | Placebo or Ca Group | | |
|-----------------------|---------------------|------------|-------------------------|-----------------------------------|-------------------|------------------|-------------------------------|------------------------------------|------|---------------------|------------------------------------|------|
| | | | | | | | n | Mean change from baseline | SD | n | Mean change from baseline | SD |
| Trang | 1998 ²³⁶ | adults | 42 | 4000 | 0 | 0.5 | 24 | 23.3 | 17.5 | 24 | 3.0 | 19.8 |
| Chan | 1982 ²³⁷ | children | 43 | 400 | 0 | 6 | 30 | 22.5 | 6.6 | 30 | -2.5 | 6.6 |
| El-Hajj (Fuleihan) | 2006 ³⁵ | children | 35 | 200 | 0 | 12 | 58 | 7.5 | 19.8 | 55 | 5.0 | 18.8 |
| El-Hajj (Fuleihan) | 2006 ³⁵ | children | 35 | 2000 | 0 | 12 | 55 | 59.9 | 67.1 | 55 | 5.0 | 18.8 |

^A Calcium supplement was given to all patients

The format of this table has been slightly modified to fit each RCT in one line.

Outcomes for Tolerable Upper Intake Levels

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

Results of all-cause mortality and cancer have been described in previous sections. In brief, we did not find vitamin D and/or calcium associated with an increased risk of mortality. For cancer risk, there were some observational studies reporting high calcium intake may be associated with an increased risk of prostate cancer (see “Prostate cancer” in “Calcium and cancer” section). We did not identify any studies on soft tissue calcification and tolerable upper intake levels.

Renal Outcomes

The WHI trial on women aged 50 to 79 years, examined the effect of vitamin 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 percent CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.⁷¹ It should be noted that women in both groups were allowed to take additional vitamin D supplements up to 600 IU and later 1000 IU per day and calcium supplements up to 1000 mg per day. The baseline total calcium intakes (from foods and supplements) were high: 34 percent consumed less than 800 mg/d, 26 percent consumed 800 to 1200 mg/d, and 40 percent consumed more than 1200 mg/d. A prior publication from WHI trial provided the same data on the risk of renal stones was also included in the Ottawa EPC report.

No studies were identified that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

Adverse Events Reported in RCTs.

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

Five RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods.^{35,51,227,238,239} Of these, one RCT administered combination of vitamin 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 107). Excessive gas, bloating, and gastrointestinal discomforts were reported to be associated with calcium supplementation (doses ranged from 600 to 1000 mg/d). Other RCTs of vitamin D (doses ranged from 400 to 5714 IU/d vitamin 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, upset stomach, musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, renal calculi and craniofacial changes. One RCT reported some adverse events that required hospital admission, including retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack (all 3 cases in vitamin D 400 IU/d plus exercise training group) and one case of acute cholecystitis (in calcium, vitamin D plus exercise training group).⁸⁰ Another RCT reported that “there were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke)” (actual data not provided), and one participant died during the study.⁹⁸ However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study. Also described earlier in the “Renal outcomes” section, the WHI trial examined the effect of vitamin 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 percent CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.⁷¹

Ottawa EPC report:

A total of 22 trials reported data on toxicity-related outcomes, 21 of which used doses above 400 IU/d. Toxicity results from trials with intakes of vitamin D above current reference intakes varied and this may have been related to different doses, baseline characteristics of populations or exposure times. Most trials excluded subjects with renal insufficiency or hypercalcemia, were of small sample sizes and had short durations of exposure to vitamin D. Event rates were low across trials in both the treatment and placebo arms.

Table 107. Adverse events reported in RCTs

| Author Year | N enrolled | Vit D dose (IU/d) | Ca dose (mg/d) | Duration | Adverse Event data (n=case#) |
|------------------------------------|------------|--|----------------|--------------------------------|--|
| Yamamoto 1995 ¹¹⁷ | 471 | 0 | 1000 | 6 mo | Comparing calcium group to the placebo group, excessive gas and bloating were more frequently reported by white women at 3 months and by whites, in general, at 6 months, and white men reported more loose stools at 6 months. |
| Moschonis 2006 ²¹⁵ | 112 | 300 D ₃ | 600 or 1200 | 12 mo | Bloating, constipation and intestinal discomfort apparently related to the calcium supplement |
| Bunout 2006 ⁸⁰ | 96 | 400 | 800 | 9 mo | Adverse events that required hospital admission: Vit D plus exercise training group (n=3): retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack. Calcium, Vit D plus exercise training group (n=1): acute cholecystitis |
| Wactawski-Wende 2006 ⁷¹ | 36282 | 400 | 1000 | 7 y | The WHI trial found an increase in the risk of renal stones (Hazard Ratio 1.17 95% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure. |
| Burleigh 2007 ⁸¹ | 205 | 800 D ₃ | 1200 | Median 1 mo | Hypercalcemia (n=2) |
| Lappe 2008 ²⁰⁸ | 5201 | 800 | 200 | 8 wks | GI disruption such as constipation, diarrhea, upset stomach (4%), and musculoskeletal soreness (0.9%) |
| Brooke 1980 ³⁴ | 126 | 1000 | 0 | 3 rd trimester only | Vit D group (craniotabes, n=2), placebo group (hypocalcemia, n=5; craniotabes, n=6) |
| Lappe 2007 ⁵² | 1180 | 1000 D ₃ | 1400-1500 | 4 y | Renal calculi in placebo (n=1), renal calculi in calcium only (n=3), renal calculi in calcium plus vit D (n=1) |
| Mastaglia 2006 ²⁴⁰ | 65 | 5000 or 10,000 D ₂ | 500 | 3 mo | Hypercalciuria (n=1) in control group |
| Zhu2008 ⁹⁸ | 256 | 1000 D ₂ | 1200 | 12 mo | There were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke). There were 8 and 5 adverse events in vitamin D and the control groups, respectively. One participant in the vitamin D group had mild asymptomatic hypercalcemia one occasion. No case of renal calculus was reported. 1 participant was deceased during the study. |
| Sneve 2008 ⁵⁰ | 445 | Group 1: 2 capsules of vitamin D ₃ each 20,000 IU taken twice a week (Monday and Thursday): ~5714 IU/d Group 2: 1 capsules of vitamin D ₃ each 20,000 IU taken twice a week (Monday and Thursday): ~2857 IU/d | 500 | 12 mo | Primary hyperparathyroidism (n=2), increase in serum calcium to 2.62 mmol/L (n=1), transient increases in serum calcium > 2.59 mmol/L (n=4). 317 other adverse events were recorded, most of them related to GI discomfort. There were no significant differences between the treatment groups regarding adverse events. |

Chapter 4. Discussion

This evidence report on vitamin D and calcium in relation to health outcomes was prepared for consideration by the Committee on Dietary Reference Intakes for Vitamin D and Calcium at the request of AHRQ on behalf of the various sponsors. This report does not make nor was it intended to make recommendations for DRI values concerning vitamin D or calcium. Responsibility for setting DRI values lies with the Committee. Evidence from systematic reviews is one of several types of information available to the Committee for use in its deliberations to establish DRI values. This is the first time that an independent systematic review is being commissioned to support the DRI process. Thus, it is important for users of this report to fully appreciate the nuances of the methodologies employed, as well as the strengths and limitations of this approach. In particular, it should be noted that total vitamin D exposure was not evaluated in this report because there is no valid method to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure and it is also the TEP's consensus that vitamin D intake, as estimated by current food frequency questionnaires, is too inaccurate to be of value.

For this report, we identified 165 primary articles that met the eligibility criteria established by the TEP. In addition, we included 11 published systematic reviews that incorporated over 200 additional primary articles. Despite the relatively large number of studies included, with the following few exceptions, it is difficult to make any substantive and concise statements on the basis of the available evidence concerning the association of serum 25(OH)D concentration, supplemental vitamin D, dietary calcium intake, or the combination of both nutrients with the various health outcomes. It proved challenging because many of the studies contained substantial heterogeneity and their findings were inconsistent for the health outcomes examined.

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

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

For growth, a meta-analysis of 17 RCTs did not find a significant effect on weight and height gain attributable to calcium supplement in children ranged from 3 to 18 years of age.

For bone health, one well-conducted systematic review of RCTs found that vitamin 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.

For breast cancer, subgroup analyses in four cohort studies consistently found that calcium intake in the range of 780 to 1750 mg/d in premenopausal women was associated with a decreased risk for breast cancer. However, no RCTs of calcium supplementation to prevent breast cancer in premenopausal women have been published. In contrast, cohort studies of postmenopausal women are consistent in showing no association of calcium intake with the risk of breast cancer.

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

For cardiovascular events, a cohort study and a nested case-control study found associations between lower serum 25(OH)D concentrations (less than either about 50 or 75 nmol/L) and

increased risk of total cardiovascular events; however an RCT found no effect of supplementation and studies of specific cardiovascular events were too sparse to reach conclusions. Taken together, six cohort studies of calcium intake suggest that in populations at relatively increased risk of stroke and with relatively low dietary calcium intake (i.e., in East Asia), lower levels of calcium intake under about 700 mg/day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the US, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1000 mg.

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

Strengths of This Report

The strengths of this report lie in the wide range of topics covered, critical appraisal, detailed documentation, transparent methods to assess the scientific literature, and an unbiased selection of studies. A team of evidence-based methodologists not previously directly involved in research related to vitamin D and calcium worked with nutrient experts to refine the key questions (initially defined by AHRQ with input from various sponsors), analytic framework, and review criteria for the systematic review. After defining the questions and eligibility criteria with input from content experts and the sponsoring agencies, the Tufts EPC reviewed the published evidence on the topic. The intent was to perform a thorough and unbiased systematic review of the literature base on available evidence as defined by prespecified criteria. Once the review process began, input from experts in the field was sought to clarify technical questions during the literature review process. These individuals did not participate in study selection or detailed data extraction from the included studies nor were any members serving on the IOM committee on vitamin D and calcium involved in the review of this document. A quality rating as detailed in Chapter 2 (Methods section) was assigned for each primary study and systematic review, and incorporated into the data summaries section of the report. On the basis of this work, a sound foundation has been created which will facilitate rapid and efficient future updates as needed.

Details concerning the process of question formulation, selection of health outcomes of interest, justification for study selection criteria, methods used for critical appraisals of studies and quality rating, and summary of results are described fully in the Methods chapter. This approach is critical to the establishment of a transparent and reproducible process. Furthermore, important variables that affect vitamin D status such as life stages, latitude of the study locale, background diet and skin pigmentation are documented in this review.

This evidence report was carried out under the AHRQ EPC program, which has a 12-year history of producing over 175 evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continuously refine approaches to conducting systematic reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. In addition, the Tufts EPC has conducted a number of nutrition-related evidence reports^{19-22,241}, as well as

conducted the mock exercise on vitamin A panel.³ This report drew on these experiences, the expertise of the TEP, and the support of federal agencies.

DRI and the Literature on Vitamin D and Calcium

It should be emphasized that none of the studies reviewed were designed to address issues specifically relevant for establishing DRI values (i.e., to ascertain the optimal dose in a particular life stage to promote growth and tissue maintenance, and prevent chronic disease throughout the lifecycle). In general, the studies did not enroll subjects with ages that could be easily mapped to specific life stages as defined within the DRI framework (with the exception of postmenopausal women and pregnant or lactating women) and did not evaluate health outcomes on the basis of what doses will lower risk for a particular disease in prespecified life stages. Therefore, data will need to be extrapolated from these studies to craft a set of DRI values for vitamin D and calcium. This extrapolation may prove challenging.

Certain issues concerning the studies of vitamin D must be noted. As mentioned previously, it is difficult to evaluate nutritional adequacy because there are no methods currently available to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure on an individual or group level. In addition, it is generally accepted that estimating intake by dietary assessments is not a valid indicator of vitamin D status, because there are limitations in the completeness of nutrient databases for both food and dietary supplements vitamin D content and the rapidly changing landscape of vitamin D food fortification has not yet been captured in either instruments used to assess intake and the databases used to analyze the data. For example, vitamin D values are available for only about 600 out of 1400 foods in the USDA National Nutrient Database for Standard Reference (<http://www.ars.usda.gov/nutrientdata>) and notably missing are foods recently fortified with vitamin D.²⁵ Given the recent trend towards increased nutrient fortification of the North American food supply, the lag in updating food composition tables, and the inability to distinguish between fortified and unfortified foods when using most dietary assessment tools, it is difficult to accurately estimate dietary intakes of vitamin D, especially for a given year. Shifts in methodological approaches to measure serum 25(OH)D concentrations, the heterogeneous nature of the data available with respect to study locations (i.e., latitude) and times during the year (i.e., season) hamper our ability to succinctly summarize dose-response relationships. We did not perform a dose-response meta-analysis of the relationship between serum 25(OH)D concentrations and health outcomes because limited and inconsistent data would result in a meta-analysis that is difficult to interpret and results that may be misleading. Furthermore, many of the large cohorts analyzed for associations of vitamin D with health outcomes enrolled mostly white participants aged approximately 40 to 70 years old and much of the data on intake dose-response and serum 25(OH)D concentration were derived from studies designed to measure bone health in postmenopausal women. These factors limit the applicability of the findings to other life stages and other racial groups.

Unlike serum 25(OH)D concentrations for vitamin D, there is no equivalent serum biomarker to indicate calcium status. Relying on dietary assessment to gauge calcium intake is limited by the confounding effect of vitamin D status on the efficiency of calcium absorption and uncertainties in the calcium content of many foods due to the recent trend in nutrient fortification of food, limited ability of current dietary assessment tools to distinguish among fortified and unfortified foods and the lag in updating nutrient databases with current nutrient information.

Limitations of our Methodological Approach

The number of potentially relevant (English language articles on humans and not reviews) vitamin D studies indexed in MEDLINE is very large (~15,000) and the number of calcium studies is even larger (~110,000). Without unlimited time and resources, the systematic review conducted in this report had to focus on selected key questions predefined by our federal sponsors with input from the IOM, and capitalize on existing systematic reviews. Using previous systematic reviews risks propagating deficiencies and errors²⁴² 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 AMSTAR²⁶ checklist, we cannot reliably know the validity of the reported summary data without knowing the details of the primary studies. It should also be stressed that a well-performed systematic review does not necessarily imply that the body of evidence for a particular outcome of interest is of high quality. While some systematic reviews assessed the quality of the individual studies, the methods used varied. Any systematic review is limited by the quality of the primary studies included in the review. Unless the methods used to assess the quality of the primary studies is transparent and the details made available for examination, it would be difficult to reliably determine the validity of the conclusions. Also, relying on existing systematic reviews alone could have potentially precluded us from identifying all relevant studies because those systematic reviews might have addressed somewhat different questions and had a different scope from this review. For example, for growth outcome in children, we principally relied on the findings from a meta-analysis of RCTs of calcium originally designed to evaluate bone density outcomes. If there were RCTs of calcium intake specifically designed to measure growth outcomes such as weight and height gain, but not bone density, then those studies would not have been identified. In addition, as per the task order from AHRQ, we relied on the Ottawa report for bone health outcomes and we did not examine specific studies included in that report. As a consequence, if those studies had reported other (than bone health) outcomes that were of interest, those studies would not have been included in this review.

As there is no consensus on how to assess the quality of the nutrition observational studies, we created a quality checklist based on a newly published reporting standard for observational studies³² and nutrition reporting items that we believe should be considered in quality assessment. This checklist, however, has not been calibrated and the intra- and interrater variability have not been assessed. We should also remind the readers that impeccable study reporting does not equate study validity. However, transparent, comprehensive, and accurate reporting does help in evaluating a study's validity.

Also, studies on vitamin D and calcium were not specifically targeted at life stages (except for children, pregnant, and postmenopausal women) specified for the determination of DRI. We, therefore, were unable to structure our report strictly according to prespecified life stages. When a study enrolled populations that spanned across multiple life stages, we provided our best estimates as to which life stage(s) the study's findings would be of most relevance.

Comments on the Observational Studies

All the included observational studies were designed to generate hypotheses of potential associations of multiple factors with vitamin D or calcium. Therefore, a finding of a significant association in these studies, after exploratory analyses, should not be considered equivalent to

the result of studies that were designed to confirm this relationship. Many of the nested case-control studies typically excluded a substantial portion of participants (some as high as 60 to 70 percent) in the original cohorts because blood samples, or completed dietary questionnaires were not available. How this selection bias would affect the reported association is unclear. In addition, several of the studies might have suffered from outcome misclassification; for example, when cancer cases were identified from registries without histopathology verification. The effect of outcome misclassification is unpredictable. Furthermore, many of the studies did not report a power calculation. Even though many of the studies included cohorts with relatively large numbers of subjects (tens of thousands), it is plausible that, in fact, the included studies may have been underpowered to detect the true effect sizes. If that were the case, the significant effect reported may, in fact, be spurious. Furthermore, many of the reported effect sizes were small to moderate (with OR ranged from 1.03 to 2.0). When the effect size is small, the possibility of residual confounding by unmeasured variables must be considered.

Sources of Heterogeneity and Potential Biases

As have been mentioned previously, most of the findings reported in this review were inconsistent for each of the outcomes of interest. Many studies showed substantial heterogeneity. Some studies adjusted the serum 25(OH)D concentration by season of serum collection, some did not. While the majority of the studies used some forms of RIA to measure the serum 25(OH)D concentration, a minority used competitive protein-binding assay. Some studies reported a substantial proportion of the frozen serums were accidentally thawed and limited the analyses that could be performed. It is unclear how this would alter the overall results. Many studies suffered from potentially inadequate outcome ascertainment (e.g., reliance on self-reported calcium intake and hypertension diagnosis). Time between measurement of serum 25(OH)D concentration and the diagnosis of interest varied. For prostate and colorectal cancer, it ranged from 1 to more than 16 years. Factors potentially relevant to the outcomes of interest like family history (in colorectal cancer) were not consistently reported and accounted for in the studies. Also, the blinding of case assessors to the risk factor of interest (e.g., serum 25(OH)D concentrations) as well as that of investigators who measured the risk factor *per se* to outcomes were rarely reported.

For studies on calcium supplementation, intake compliance, information on the bioavailability of the calcium source, the role of background sun exposure, and associated vitamin D effects were not consistently available across all studies. Thus, it is difficult to interpret those findings on an absolute level and among studies.

Finally, all systematic reviews, including this report, may suffer from potential publication and reporting biases since currently there is no reliable way to detect and correct these biases. However, there is an underlying suspicion of publication bias against studies having either null or negative outcomes and reporting bias toward “significant” outcomes in the literature.^{243,244} Thus, it is important to consider these biases when reviewing the overall findings of any systematic review.

Vitamin D Intake and Response in Serum 25(OH)D Concentration

The findings of this review on the association between vitamin D intake dose and change in serum 25(OH)D concentration was primarily derived from RCTs reviewed in a systematic review of bone health in postmenopausal women. This limits the applicability of the findings to

other life stages. Though, we did not find any reason to consider these trials to be biased, they are nonetheless an arbitrary sample of all studies that have reported the association between vitamin D intake dose and change in serum 25(OH)D concentration. We did not perform a quantitative synthesis (e.g., meta-regression) to examine the relationship between vitamin D intake dose and serum 25(OH)D concentration due to the heterogeneity across studies. Studies had varied compliance rates in the vitamin D intake; limited or no adjustment for skin pigmentations, calcium intake, or background sun exposure; different vitamin D assay methodologies and measurement (both intra- and interassay) variability. All these factors increase the heterogeneity and limit the usefulness of an overall summary estimate for an intake dose response in serum 25(OH)D concentration. Nonetheless, overall, there appeared to be a trend for higher vitamin D supplementation dose resulting in higher net change in serum 25(OH)D concentration.

Considerations for Future DRI Committees

Formulating the appropriate key questions is the most important aspect of conducting a systematic review to ensure the final product will meet the intended purpose. Ideally, this should be an iterative process involving the sponsors, EPC, TEP and targeted end-users. The questions should be reviewed and potentially refined once the “state” of the literature has been systematically appraised, with the understanding that any modifications to the key questions after the review process has started will likely extend the literature review and synthesis processes. In addition, developing relevant study selection criteria for the systematic review is critical to finding pertinent data to answer the key questions; the TEP should be engaged early in this process. Crafting a framework of the entire review process depicting the explicit roles of the sponsors, TEP, and targeted end-users could also be helpful for future reviews.

While the process of conducting the actual systematic review of a nutrient or group of nutrients on an agreed upon set of key questions concerning specific health outcomes is carefully laid out and could be replicated without undue difficulty, the process of selecting which health outcomes would be important for inclusion in a systematic review could not be easily replicated. The health outcomes selected were decided after much deliberation by the TEP with input from the various partners. As the nature of the deliberation hinged much on the expertise reflected by the particular composition of the TEP, it is conceivable that a different TEP composed of members with different expertise may have recommended a different set of health outcomes for inclusion. To minimize this variability, an a priori designed set of instructions to weigh each outcome (taking into account such factors like population attributable risk, morbidity, and others) for possible inclusion would be valuable.

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Abbreviations

| | |
|-----------|---|
| 25(OH)D | 25-hydroxyvitamin D |
| AHRQ | Agency for Healthcare Research and Quality |
| AMSTAR | Assessment of multiple systematic reviews |
| Anthrop | Anthropometric measures |
| ASA | Acetyl-salicylic acid (aspirin) |
| ATBC | Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study |
| BCDDP | Breast Cancer Detection Demonstration Project |
| BMC | Bone mineral content |
| BMD | Bone mineral density |
| BMI | Body Mass Index |
| Ca | Calcium |
| CABG | Coronary artery bypass graft |
| CeVD | Cerebrovascular disease |
| CHD | Coronary heart disease |
| CHD | Coronary Heart Disease |
| CI | Confidence Interval |
| CIFOS | Calcium Intake Fracture Outcome Study |
| CONSORT | Consolidated Standards of Reporting Trials |
| CPBA | Competitive protein binding assay |
| CPEP | Calcium for Prevention of Preeclampsia Trial |
| CPP | Calcium Polyp Prevention Study |
| CPS | Cancer Prevention Study |
| CRC | Colorectal cancer |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| Demograph | Demographics |
| DM | Diabetes Mellitus |
| DRI | Dietary Reference Intake |
| Dx | Diagnosis |
| EAR | Estimated average requirement |
| EPC | Evidence-based Practice Center |

| | |
|-------------|---|
| FFQ | Food frequency questionnaire |
| FNB | Food and Nutrition Board |
| FOS | Framingham Offspring Study |
| FREE | Fracture Risk Epidemiology in the Elderly |
| HAH | Harvard Alumni Health Study |
| HbC | Hemoglobin C disease |
| HPFS | Health Professionals Follow-up Study |
| HPLC | High pressure liquid chromatography |
| HR | Hazard ratio |
| ht | Height |
| HT | Hormone (replacement) therapy |
| HTN | Hypertension |
| IHD | Ischemic heart disease |
| IOM | Institute of Medicine |
| Iowa WHS | Iowa Women's Health Study |
| IQR | Interquartile range |
| IU | International unit |
| Japan CC | Japan Collaborative Cohort |
| Japan PHC | Japan Public Health Center study |
| Kupio ORFPS | Kupio Osteoporosis Risk Factor and Prevention Study |
| MCS | Multiethnic Cohort Study, Hawaii, California |
| MI | Myocardial infarction |
| mil | Million |
| mo | Months(s) |
| N | Number of subjects |
| n | Number of subjects had event(s) |
| NA | Not applicable |
| nd | No data |
| NHANES | National Health and Nutrition Examination Survey |
| NHEFS | NHANES I Epidemiologic Follow-up Study |
| NHS | Nurses' Health Study |

| | |
|----------|---|
| NIH | National Institutes of Health |
| NIH-AARP | National Institutes of Health – American Association of Retired Persons |
| NPC | Nutrition Prevention of Cancer trial |
| NS | Not significant |
| ODS | Office of Dietary Supplements |
| OR | Odds Ratio |
| PAHSG | Princess Anne Hospital Study Group, UK |
| PCI | Percutaneous coronary intervention |
| PHS | Physicians’ Health Study |
| PI(E)CO | Population, Intervention (or Exposure), Comparison and Outcome |
| PLCO | Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial |
| PMID | PubMed (unique) identifier |
| PSA | Prostate specific antigen |
| PTH | Parathyroid hormone |
| RCT | Randomized-controlled trial |
| RDA | Recommended Dietary Allowance |
| RIA | Radioimmunoassay |
| RR | Relative risk |
| SBP | Systolic blood pressure |
| SD | Standard deviation |
| SE | Standard error |
| STROBE | STrengthening the Reporting of OBservational studies in Epidemiology |
| Subgp | Subgroup |
| Suppl | Supplement(s) |
| TEP | Technical Expert Panel |
| TIA | Transient ischemic attack |
| TOHP | Trials of Hypertension Prevention |
| TOO | Task order officer |
| UK | United Kingdom |
| UL | Tolerable upper intake levels |
| US | United States |
| USDA | United States Department of Agriculture |

| | |
|-----|---------------------------|
| UV | Ultraviolet rays |
| Vit | Vitamin |
| WCC | Washington County Cohort |
| WHI | Women's Health Initiative |
| WHS | Women's Health Study |
| wk | week(s) |
| WMD | Weighted mean difference |
| wt | Weight |
| y | Year(s) |

Latitudes of Selected Cities

| Latitude | Western Hemisphere | Eastern Hemisphere |
|----------|--|--|
| 64° N | Reykjavik, Iceland Nome, Alaska | |
| 60-61° N | Anchorage, Alaska | Oslo, Norway |
| 56° N | | Copenhagen, Denmark |
| 52° N | | Berlin, Germany Amsterdam, Netherlands |
| 51° N | Calgary, Alberta | London, England |
| 49° N | Vancouver, British Columbia | Paris, France |
| 48° N | Seattle, Washington | Munich, Germany |
| 47° N | Quebec City, Quebec Bismarck, North Dakota | Zurich, Switzerland |
| 45° N | Ottawa, Ontario Minneapolis, Minnesota | Milan, Italy |
| 44° N | Toronto, Ontario Portland, Maine | |
| 42° N | Boston, Massachusetts Chicago, Illinois | Rome, Italy |
| 41° N | New York, New York Salt Lake City, Utah | Barcelona, Spain |
| 40° N | Philadelphia, Pennsylvania Columbus, Ohio Washington, DC | Madrid, Spain Beijing, China |
| 39° N | St Louis, Missouri Sacramento, California Louisville, Kentucky | |
| 38° N | Wichita, Kansas San Francisco, California | Athens, Greece |
| 36° N | Raleigh, North Carolina Las Vegas, Nevada | Tokyo, Japan |
| 34° N | Columbia, South Carolina Los Angeles, California | Fez, Morocco |
| 33° N | Dallas, Texas | |
| 30° N | New Orleans, Louisiana | Cairo, Egypt |
| 29° N | San Antonio, Texas | New Delhi, India |
| 26° N | Miami, Florida | |
| 22° N | | Hong Kong, China |
| 21° N | Honolulu, Hawaii | |
| 19° N | Mexico City, Mexico | Mumbai (Bombay), India |
| 15° N | Guatemala City, Guatemala | Manila, Philippines |
| 10° N | Caracas, Venezuela | |
| 4° N | Bogota, Columbia | |
| 1° N | | Singapore |
| 12° S | Lima, Peru | |
| 23° S | Rio de Janeiro, Brazil | |
| 26° S | | Johannesburg, South Africa |
| 34° S | | Sydney, Australia Cape Town, South Africa |
| 35° S | Buenos Aires, Argentina | |
| 37° S | | Auckland, New Zealand |
| 38° S | | Melbourne, Australia |
| 41° S | | Wellington, New Zealand |

Appendix A. Search strategy for primary studies

a. Overall Search Strategy for Outcomes of Estimated Average Requirements

Database: Ovid MEDLINE(R), CCTR (1969 to April 2009)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
4. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/
9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol\$.tw.
12. Cholecalciferol/
13. Cholecalciferol\$.tw.
14. calciferol.tw.
15. or/1-14
16. exp Calcium/
17. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
18. exp Calcium, Dietary/
19. calcium.tw.
20. or/16-19
21. (ANIMALS not HUMAN).sh.
22. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
23. 15 or 20
24. 23 not 21
25. 24 not 22
26. limit 25 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or "review")
27. 25 not 26
28. limit 27 to english language
29. randomized controlled trial.pt.

30. controlled clinical trial.pt.
31. randomized controlled trials/
32. Random Allocation/
33. Double-blind Method/
34. Single-Blind Method/
35. clinical trial.pt.
36. Clinical Trials.mp. or exp Clinical Trials/
37. (clinic\$ adj25 trial\$).tw.
38. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw.
39. Placebos/
40. placebo\$.tw.
41. random\$.tw.
42. trial\$.tw.
43. (latin adj square).tw.
44. Comparative Study.tw.
45. exp Evaluation studies/
46. Follow-Up Studies/
47. Prospective Studies/
48. (control\$ or prospectiv\$ or volunteer\$).tw.
49. Cross-Over Studies/
50. or/29-49
51. 50 and 28
52. 28 not 51
53. limit 51 to yr="1969-2008"
54. limit 52 to yr="1969-2008"
55. 53 not ("200810\$" or "200811\$" or "200812\$").ed.
56. 54 not ("200810\$" or "200811\$" or "200812\$").ed.
57. 55 or 56
58. exp Vitamin D/
59. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
60. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
61. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
62. 25-hydroxycholecalciferol.tw.
63. 25-hydroxyergocalciferol.tw.
64. calcidiol.tw.
65. Calcifediol/
66. (vit adj (d or d2 or d3)).mp.

67. Ergocalciferols/
68. Ergocalciferol\$.tw.
69. Cholecalciferol/
70. Cholecalciferol\$.tw.
71. calciferol.tw.
72. or/58-71
73. exp Calcium/
74. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
75. exp Calcium, Dietary/
76. calcium.tw.
77. or/73-76
78. (ANIMALS not HUMAN).sh.
79. (ANIMALS not HUMAN).sh.
80. 72 or 77
81. 80 not 78
82. 81 not 79
83. limit 82 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or "review")
84. 82 not 83
85. limit 84 to english language
86. randomized controlled trial.pt.
87. controlled clinical trial.pt.
88. randomized controlled trials/
89. Random Allocation/
90. Double-blind Method/
91. Single-Blind Method/
92. clinical trial.pt.
93. Clinical Trials.mp. or exp Clinical Trials/
94. (clinic\$ adj25 trial\$.tw.
95. ((singl\$ or doubl\$ or treb1\$ 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. Osteoporos\$.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. (elevat\$ adj2 blood pressure).tw.
217. systolic blood pressure/
218. diastolic blood pressure/
219. mean arterial pressure/
220. or/212-219
221. limit 220 to "all adult (19 plus years)"
222. exp Neoplasms/dh, pc, et, di, ep [Diet Therapy, Prevention & Control, Etiology, Diagnosis, Epidemiology]
223. ("cancer risk" or "melanoma risk" or "lymphoma risk" or "leukemia risk" or "myeloma risk" or "sarcoma risk").tw.
224. (("risk of" or "occurrence of") and (cancer\$ or neoplasm\$ or malignan\$ or adenocarcinom\$ or carcinom\$ or melanom\$ or lymphom\$ or leuk?emi\$ or myelodysplas\$ or myelom\$ or sarcom\$)).tw.
225. 222 or 224 or 223
226. colon polyps.mp. or exp adenomatous polyps/ or exp colonic polyps/
227. (colon\$ or rectum or rectal or colorectum or colorectal).ti,ab.
228. (adenoma\$ or polyps or polyp).ti,ab.
229. 228 and 227
230. 229 or 226
231. mammography.mp. or exp mammography/
232. mammog\$.ti,ab.
233. 231 or 232
234. dens\$.ti,ab.
235. 233 and 234
236. prostate specific antigen.mp. or exp prostate-specific antigen/
237. (aberrant crypt\$ foc\$ or ACF).ti,ab.
238. (prostat\$ and (intraepitheli\$ or intra-epitheli\$ or intra epitheli\$) and Neoplas\$).ab,ti.
239. 236 or 238 or 235 or 237 or 230
240. type 1 diabetes mellitus.mp. or exp Diabetes Mellitus, Type 1/
241. psoriasis.mp. or exp Psoriasis/
242. rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/
243. multiple sclerosis.mp. or exp Multiple Sclerosis/
244. inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
245. ulcerative colitis.mp. or exp Colitis, Ulcerative/

246. Crohn's disease.mp. or exp Crohn Disease/
 247. 240 or 241 or 242 or 243 or 244 or 245 or 246
 248. tuberculosis.mp. or exp Tuberculosis/
 249. influenza.mp. or exp Influenza, Human/
 250. 248 or 249
 251. exp "Activities of Daily Living"/
 252. muscle strength.mp. or exp Muscle Strength/
 253. exp Musculoskeletal Equilibrium/ or exp Walking/
 254. ("balance test" or "timed walk" or "physical performance" or "hand-grip strength").tw.
 255. exp Hand Strength/
 256. exp Muscles/
 257. ("walking time" or "muscle strength").tw.
 258. or/251-257
 259. limit 258 to ("all adult (19 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
 260. exp Pre-eclampsia/
 261. (pre-eclampsia or preeclampsia).mp.
 262. pregnancy complication\$.mp. or exp Pregnancy Complications/
 263. or/260-262
 264. limit 263 to male
 265. limit 263 to female
 266. 264 not 265
 267. 263 not 266
 268. limit 267 to animal
 269. limit 267 to human
 270. 268 not 269
 271. 267 not 270
 272. limit 271 to english language
 273. exp infant,low birth weight/
 274. low birth weight.af.
 275. exp infant, premature/
 276. ("small for gestational age" or sga).af.
 277. ((preterm or prematur\$) adj6 (infant or newborn)).af.
 278. or/273-277
 279. exp Milk, Human/
 280. human milk.mp.
 281. (human adj2 milk).tw.
 282. breast milk.mp.
 283. breastmilk.mp.

284. breast feeding.mp.
285. breastfeed\$.mp.
286. breast fed.mp.
287. breastfed.mp.
288. (breast adj2 fed).tw.
289. exp lactation/
290. (lactating or lactation).mp.
291. or/279-290
292. Mortality.mp. or exp Mortality/
293. Fatal Outcome.mp. or exp Fatal Outcome/
294. exp Death/ or exp "Cause of Death"/ or death.mp.
295. Survival Rate.mp. or exp Survival Rate/
296. 295 or 292 or 294 or 293
297. heterotopic ossification.mp. or exp Ossification, Heterotopic/
298. myositis ossificans.mp. or exp Myositis Ossificans/
299. calcinosis.mp. or exp Calcinosis/
300. extraosseous calcification.mp.
301. metaplastic calcification.mp.
302. myo-osteosis.mp.
303. neurogenic osteoma.mp.
304. osseous heteroplasia.mp.
305. ossifying fibromyopathy.mp.
306. para-articular calcification.mp.
307. heterotopic calcification.mp.
308. pathological bone.mp.
309. pathological calcification.mp.
310. periarticular calcification.mp.
311. synostosis.mp.
312. ectopic bone.mp.
313. heterotopic bone.mp.
314. dystrophic ossification.mp.
315. ectopic ossification.mp.
316. metaplastic ossification.mp.
317. para-articular ossification.mp.
318. periarticular ossification.mp.
319. pathological ossification.mp.
320. ectopic calcification.mp.
321. soft tissue calcification.mp.

322. (vascular adj3 calcification).mp.
323. (aort\$ adj3 calcification).mp.
324. (valv\$ adj3 calcification).mp.
325. or/297-324
326. limit 325 to animal
327. limit 325 to human
328. 326 not 327
329. 325 not 328
330. limit 329 to english language
331. exp kidney disease/
332. exp kidney/
333. kidney.mp.
334. renal.af.
335. nephro\$.af.
336. exp renal replacement therapy/
337. exp kidney, artificial/
338. (hemodialy\$ or haemodialy\$ or dialy\$).af.
339. exp Kidney Glomerulus/
340. exp Kidney Function Tests/
341. ur?emia.tw.
342. exp Kidney Calculi/
343. (kidney stone\$ or renal stone\$ or renal calcul\$ or kidney calcul\$ or nephrolith\$).af.
344. 343 not 342
345. exp nephrolithiasis/
346. or/331-345
347. allerg\$.mp. or exp Hypersensitivity/

b. Overall Search Strategy for Outcomes of Upper Limits

Database: Ovid MEDLINE(R), CCTR (from 1966 to December 2008)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
4. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/

9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol\$.tw.
12. Cholecalciferol/
13. Cholecalciferol\$.tw.
14. calciferol.tw.
15. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
16. or/1-15
17. supplement\$.tw.
18. exp Dietary Supplements/to, ae, po, ut [Toxicity, Adverse Effects, Poisoning, Utilization]
19. No-Observed-Adverse-Effect Level/
20. upper limit\$.tw.
21. UL.tw.
22. (excess\$ or toxic\$).tw.
23. vit d intoxic\$.tw.
24. (noael or noel).tw.
25. (no observed adj2 effect\$).tw.
26. or/17-25
27. 26 and 16
28. (ANIMALS not HUMAN).sh.
29. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
30. 27 not 28
31. 30 not 29
32. limit 31 to (addresses or bibliography or biography or comment or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or "review")
33. 31 not 32
34. limit 33 to english language
35. exp kidney disease/
36. exp kidney, artificial/
37. exp Kidney Function Tests/
38. ur?emia.tw.
39. (kidney stone\$ or renal stone\$ or renal calcul\$ or kidney calcul\$ or nephrolith\$).af.
40. exp nephrolithiasis/
41. heterotopic ossification.mp. or exp Ossification, Heterotopic/
42. myositis ossificans.mp. or exp Myositis Ossificans/
43. calcinosis.mp. or exp Calcinosis/
44. extraosseous calcification.mp.
45. metaplastic calcification.mp.

46. myo-osteosis.mp.
47. neurogenic osteoma.mp.
48. osseous heteroplasia.mp.
49. ossifying fibromyopathy.mp.
50. para-articular calcification.mp.
51. heterotopic calcification.mp.
52. pathological bone.mp.
53. pathological calcification.mp.
54. periarticular calcification.mp.
55. synostosis.mp.
56. ectopic bone.mp.
57. heterotopic bone.mp.
58. dystrophic ossification.mp.
59. ectopic ossification.mp.
60. metaplastic ossification.mp.
61. para-articular ossification.mp.
62. periarticular ossification.mp.
63. pathological ossification.mp.
64. ectopic calcification.mp.
65. soft tissue calcification.mp.
66. (vascular adj3 calcification).mp.
67. (aort\$ adj3 calcification).mp.
68. (valv\$ adj3 calcification).mp.
69. or/41-68
70. Calcification, Physiologic/de [Drug Effects]
71. Hypercalcemia/
72. Kidney Calculi/
73. Nephrocalcinosis/
74. Urinary Calculi/
75. Bladder Calculi/
76. Ureteral Calculi/
77. Calcinosis/
78. Hypercalcemi\$.tw.
79. (Burnett\$ adj2 syndrome\$).tw.
80. Hypercalciuri\$.tw.
81. or/70-80
82. psoriasis.mp. or exp Psoriasis/
83. 81 or 69 or 82

84. 34 and 83

85. limit 84 to case reports

86. 84 not 85

Appendix B. Search strategy for systematic reviews

Databases: MEDLINE(R), the Cochrane Database of Systemic Reviews, and the Health Technology Assessments (up to December 2008)

1. (meta-analys\$ or metaanalys\$).mp. [mp=title, abstract, full text, keywords, caption text]
2. (systematic review\$ or systematic literature or evidence-based or evidence review\$).mp.
[mp=title, abstract, full text, keywords, caption text]
3. (EBM or EBR or EBRs).mp. [mp=title, abstract, full text, keywords, caption text]
4. or/1-3
5. (vitamin D or cholecalciferol or ergocalciferol or hydroxy vitamin D or calcitriol).mp.
[mp=title, abstract, full text, keywords, caption text]
6. Calcium.mp. [mp=title, abstract, full text, keywords, caption text]
7. 5 or 6
8. 4 and 7

Appendix D. Evaluation of existing systematic reviews and evidence tables of the qualified systematic reviews

Evaluation of existing systematic reviews

| Author Year Journal /Source | Intervention or exposure | Outcome | Study design included | Healthy population at baseline?* | Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?*** | Clear reporting of comparison and control group? | Clear reporting of outcome definitions? | Clear reporting of study designs (need separate reporting if two or more different designs are included)? | Comments* *** |
|---|-----------------------------|------------------------|--|---|---|---|---|---|--|
| Autier 2007 Arch Intern Med [17846391] ¹ | Vitamin D [+/- Calcium] | All cause mortality | RCTs | Yes ¹ | Yes | Yes | Yes | Yes | One additional study found |
| Avenell 2008 Cochrane Database of Systematic Reviews [16034849] ² | Vitamin D [+/- Calcium] | All cause mortality | RCTs | Yes | Yes | Yes | Yes | Yes | All relevant studies included in Autier 2007 – Conclusions are same as Autier 2007. |
| Allender 1996 Ann Intern Med | Ca supplement | Blood pressure | RCT | Yes (subgroup analysis) | Yes | Yes | Yes | Yes | 26 of 64 potential RCTs |
| Cappuccio 1995 AJE | Ca intake | Blood pressure | Observat ional, including cross- sectional | Unclear | No | NA (regressions) | Yes | No | REJECT Includes XS |
| Dickinson 2008 Cochrane | Ca supplement | Blood pressure | RCT | No All with HTN | Yes | Yes | Yes | Yes | Revision of 2006 SR 15/64 potential RCTs |

¹ We excluded a study on patients with congestive heart failure in our reanalysis of data from this systematic review

| Author Year Journal /Source | Intervention or exposure | Outcome | Study design included | Healthy population at baseline?* | Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?*** | Clear reporting of comparison and control group? | Clear reporting of outcome definitions? | Clear reporting of study designs (need separate reporting if two or more different designs are included)? | Comments* *** |
|--|----------------------------------|---|-----------------------------------|---|---|--|---|---|--|
| Griffith 1999 AJH | Ca supplement | Blood pressure | RCT | Yes & No HTN & NTN combined See comment | Yes | Yes | Yes | Yes | Update of Bucher 1996 [2263] Subgp analysis HTN vs NTN in Bucher only 42/64 potential RCTs |
| van Mierlo 2006 J Hum Hypert | Ca supplement | Blood pressure | RCT | Yes Subgroup of HTN & NTN | Yes | Yes | Yes | Yes | 40/64 potential RCTs |
| Trumbo 2007 Nutr Rev | Ca supplement | Blood pressure, HTN, Pregnancy- induced HTN | All | Yes Subgroup of HTN & NTN | Yes (interv) No (observ) | No | No | No | REJECT Qualitative only Count of sig studies only Unclear if SR. |
| Bergsma-Kadijk 1996 Epidemiology | Ca intake | cancer and polyp | Cohort and Case- control | nd (probably healthy population) | nd on dietary assessment method | nd on Ca intake (only RR/OR between lowest and highest categories reported) | nd | nd on the definition of case-control study | Reject |
| Weigarten 2008 Cochrane Database of Systematic Reviews | Ca supplement (>1200 mg/d) | cancer and polyp | RCT | yes (pts with prior adenoma) | yes | yes | yes | yes | Accept |

| Author Year Journal /Source | Intervention or exposure | Outcome | Study design included | Healthy population at baseline?* | Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?*** | Clear reporting of comparison and control group? | Clear reporting of outcome definitions? | Clear reporting of study designs (need separate reporting if two or more different designs are included)? | Comments* *** |
|--|--|---|-----------------------------|---|---|---|---|---|---|
| Davies 2006 J Natl Cancer Inst | Nutritional RCTs, including Ca supplement | Cancer, recurrence of preinvasive lesions | RCT | No (both pts with cancer and preinvasive lesions) | nd | no | no | yes | Part of a larger SR of both diet and physical activity on outcome among patients with cancer or preinvasive lesions |
| Bergel 2007 BMC Pediatrics | maternal calcium intake | offspring BP | RCTs & cohort | y (RCT) | no yes | yes | yes | no | Data from 2 RCTs may be useful. Reject |
| Carroll 1994 Brit J Obstet Gynecol | Ca supplement | Preeclampsia | RCT | Yes | Yes | Yes | Yes | Yes | Covered by latest Cochrane SR |
| Hofmeyer 2003 S African J | Ca Supplement | Preeclampsia | RCT | Yes | Yes | Yes | Yes | Yes | Covered by latest Cochrane SR |
| Hofmeyer 2007 S African J | Ca Supplement | Preeclampsia (and summary of the outcomes mentioned above) | RCT | Yes | Yes | Yes | Yes | Yes | Covered by latest Cochrane SR |

| Author Year Journal /Source | Intervention or exposure | Outcome | Study design included | Healthy population at baseline?* | Only included Ca +- Vit D interventions? ** Reported baseline dietary Ca intake with dietary assessment methods?*** | Clear reporting of comparison and control group? | Clear reporting of outcome definitions? | Clear reporting of study designs (need separate reporting if two or more different designs are included)? | Comments* *** |
|---|---------------------------------------|--|-----------------------------|---|---|---|---|---|--|
| Hoffmeyr 2006 Cochrane Database of Systematic Reviews | Ca supplement | Preeclampsia, pregnancy induced hypertension with and without proteinuria, maternal death or serious morbidity, other maternal outcomes, stillbirth, neonatal mortality or morbidity, preterm birth, small gestational age, and other outcomes for the child | RCT | Yes | Yes | Yes | Yes | Yes | Eligible review |
| Bucher 1996 JAMA | Ca supplement | Preeclampsia, pregnancy- induced hypertension | RCT | Yes | Yes | Yes | Yes | Yes | Covered by latest Cochrane SR |
| Gao 2005 NCI | calcium intake or dairy product | prostate cancer | prospecti ve 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- morbidity, 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 supplementati on food or chemical | weight | RCTs | yes | yes | yes | yes | yes | 2 ^o analysis of RCT of calcium on bone density outcome |
| Lanou 2008 Nutr Rev | Calcium or dairy supplementati on 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 characteristi cs reported |

*Either included only healthy population at baseline or SR had separate analyses for population with diseases and without diseases

**For SR of interventional studies

***For SR of observational studies

****Please comment on issues such as update of previous SRs or specific reasons for using or not using the SR, other than not fulfilling the screening criteria.

Evidence table of systematic review of the effect of vitamin D on bone health

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Cranney 2007 [18088161] | | |
| Design | Systematic review of RCTs and observational studies | | |
| Population | <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 (± 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 | See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail. | | |
| AMSTAR Criteria | | | |
| A priori design? | Yes | Study quality assessment performed? | No |
| Two independent reviewers? | No | Study quality appropriately used in analysis? | NA |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | No |
| Included and excluded studies listed? | No | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores) | |

Evidence table of systematic review of calcium on growth in children

| | |
|---|--|
| Author Year [PMID] | Winzenberg 2007 [17636098] |
| Design (Search Years) | Randomized controlled trials (1966-2005) |
| Population | Children <18 y |
| Intervention (Exposure) and Comparator | Supplemental and dietary calcium 300-1200 mg/d vs. placebo |
| Results | <p>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</p> |

| | | | |
|---|---|---|-----|
| 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) ² ; statistically heterogeneous DBP: -0.84 (-1.44, -0.24); statistically heterogeneous Subgroup analyses did not find that heterogeneity could be explained by age, sex, baseline calcium, dietary versus nondietary calcium, or quality. Subgroups with hypertensive versus normotensive people were significantly different (no further details). Conclusions similar to previous systematic review (Bucher 1996{2263 /id}) |

| | | | |
|---|--|--|-----|
| Comments | Update of Bucher 1996{2263 /id} (see below). | | |
| AMSTAR | | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | No |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | No |
| Study characteristics provided? | Yes | Study quality not discussed in conclusions. Funding source reported, but not conflict of interest. | |

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

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

² Numbers in parentheses are 95% confidence intervals

Evidence table of systematic review s of calcium and blood pressure. continued

| | | | | | | | | | |
|--|---|---|-----|---------------|--------------------------|--------------------------|---------------|--------------------------|--------------------------|
| Author Year [PMID] | Bucher 1996 [8596234] | | | | | | | | |
| Design (Search Years) | Randomized controlled trials (1966-1994) | | | | | | | | |
| Population | Both hypertensive and normotensive participants | | | | | | | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 406-2000 mg (41% 1000 mg; 31% 1500-1600 mg; 8% 2000 mg) | | | | | | | | |
| Results | 33 trials [Overall summary results were updated in Griffith 1999{1927 /id}, above] Studies with specified subgroups of hypertensive and normotensive participants (6 trials): <table border="0"> <tr> <td>Hypertensives</td> <td>SBP -4.30 (-6.47, -2.13)</td> <td>DBP -1.50 (-2.77, -0.23)</td> </tr> <tr> <td>Normotensives</td> <td>SBP -0.27 (-1.80, +1.27)</td> <td>DBP -0.33 (-1.56, +0.90)</td> </tr> </table> 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. | | | 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) |
| 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) | | | | | | | |
| 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) <table border="0"> <tr> <td>Hypertensives</td> <td>SBP -1.68 (-3.18, -0.18)</td> <td>DBP +0.02 (-0.96, +1.00)</td> </tr> <tr> <td>Normotensives</td> <td>SBP -0.53 (-1.56, +0.49)</td> <td>DBP -0.28 (-0.99, +0.42)</td> </tr> </table> By weighted linear regression analyses, age, sex, calcium dose, trial duration were not associated with treatment effect (P>0.10) | | | 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) |
| 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) | | | | | | | |
| 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) <table border="0"> <tr> <td>Hypertensives</td> <td>SBP +0.06 (-0.59, +0.72)</td> <td>DBP +0.03 (-0.21, +0.27)</td> </tr> </table> | | | Hypertensives | SBP +0.06 (-0.59, +0.72) | DBP +0.03 (-0.21, +0.27) | | | |
| Hypertensives | SBP +0.06 (-0.59, +0.72) | DBP +0.03 (-0.21, +0.27) | | | | | | | |
| Comments | | | | | | | | | |
| AMSTAR | | | | | | | | | |
| A priori design? | Yes | Study quality assessment performed? | No | | | | | | |
| Two independent reviewers? | nd | Study quality appropriately used in analysis? | NA | | | | | | |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | No | | | | | | |
| All publication types and languages included? | nd | Publication bias assessed? | No | | | | | | |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No | | | | | | |
| Study characteristics provided? | Yes | Excluded studies not enumerated or listed. Fixed effects models used. | | | | | | | |

Evidence table of systematic review s of calcium and blood pressure. continued

| | | | |
|--|--|--|-----|
| Author Year [PMID] | Dickinson 2006 [16625609] ³ | | |
| Design (Search Years) | Randomized controlled trials (1982-2003/2005 ⁴) | | |
| Population | Hypertensive participants | | |
| Intervention and Comparator | Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2000 mg (50% 1000 mg; 25% 1500-1600 mg; 6% 2000 mg) | | |
| Results | 13 trials SBP: -2.53 (-4.45, -0.60); statistically heterogeneous DBP: -0.81 (-2.07, +0.44); statistically heterogeneous Ca dose <1200 mg SBP -2.67 (-5.15, -0.18) DBP -0.75 (-2.13, +0.63) Ca dose 1200-2000 mg SBP -2.69 (-5.86, +0.47) DBP -0.78 (-3.82, +2.25) Not statistically significantly different by calcium dose | | |
| Comments | AMSTAR | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | Yes |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | Yes | Publication bias assessed? | Yes |
| Included and excluded studies listed? | Yes | Conflicts of interest stated? | Yes |
| Study characteristics provided? | Yes | | |

Evidence table of systematic review of calcium on growth in children

| | | | |
|--|---|---|-----|
| Author Year [PMID] | Winzenberg 2007 [17636098] | | |
| Design (Search Years) | Randomized controlled trials (1966-2005) | | |
| Population | Children <18 y | | |
| Intervention (Exposure) and Comparator | Supplemental and dietary calcium 300-1200 mg/d vs. placebo | | |
| Results | 17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) Kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity | | |
| Comments | Post hoc analysis performed on trials identified for a metaanalysis of randomized controlled trials of calcium on bone outcomes | | |
| | AMSTAR | | |
| A priori design? | Yes | Study quality assessment performed? | Yes |
| Two independent reviewers? | Yes | Study quality appropriately used in analysis? | No |
| Comprehensive literature search? | Yes | Appropriate statistical synthesis? | Yes |
| All publication types and languages included? | No | Publication bias assessed? | Yes |
| Included and excluded studies listed? | No | Conflicts of interest stated? | No |
| Study characteristics provided? | Yes | Unclear if all languages included; study quality assessed but not factored into the M-A | |

³ A technical update, with no further studies added was published in the Cochrane database in 2008.

⁴ Different dates for different databases.

Evidence table of systematic review on calcium intake and adenoma recurrence

| | |
|--|---|
| Author Year [UI] | Weingarten, 2008 [18254022] |
| Design | Randomized controlled trials: Cochrane Library Issue 2, 2007, the Cochrane Colorectal Cancer Group (CCCG) specialized register, MEDLINE (1966 to July 2007), Cancerlit (1963 to April 2002), Embase (1980 to July 2007) |
| Population | Healthy adults and studies of adults at higher risk of colon cancer due to family history, previous adenomatous polyps, or inflammatory bowel disease |
| Intervention (Exposure) and Comparator | Calcium (>1200 mg/d) vs. placebo |
| Results | Calcium vs. placebo colorectal adenoma recurrence: OR 0.74, CI 0.58-0.95, P=0.02 CRC: OR 0.34, CI 0.05-2.15, P=0.20 at least one adverse event requiring discontinuation: OR 0.93, CI 0.42-2.05, P=0.80 |
| Comments | Based only on two RCTs (1346 participants). Heterogeneity due to different dose of supplementation (one RCT supplemented with 1200 mg/d and the other RCT with 2000 mg/d). Analysis based on fixed effects model; however, considering there are only two studies, random effects model might have been more appropriate. Analysis on adverse events is based only on reported data of one out of the two RCTs (Barron 1999). Only participants with high risk due to previous adenomas were recruited in these two RCTs; therefore, applicability of the results can only be considered for high risk population. Insufficient evidence to recommend the general use of calcium supplements to prevent colorectal adenoma or colorectal cancer |
| AMSTAR | |
| A priori design? | X |
| Two independent reviewers? | X |
| Comprehensive literature search? | X |
| All publication types and languages included? | X |
| Included and excluded studies listed? | X |
| Study characteristics provided? | X |
| Study quality assessment performed? | X |
| Study quality appropriately used in analysis? | X |
| Appropriate statistical synthesis? | X |
| Publication bias assessed? | X |
| Conflicts of interest stated? | X |

Appendix E. Blank Data Extraction Form and Quality Assessment Checklists

ELIGIBILITY CRITERIA AND OTHER CHARACTERISTICS

| UI | Author Year | Study Design* | Inclusion | Exclusion | Enrollment Years | Trial or Cohort Name | Funding Source | Extractor |
|----|-------------|--|-----------|-----------|------------------|----------------------|----------------|-----------|
| | | RCT RCT-post hoc** Other intervention study Cohort study Case-cohort study | | | | | | |

*Leave appropriate choice of study design and delete all others

**Post hoc analyses of an existing RCT for outcomes that were not planned in the original RCT

POPULATION (BASELINE)**

| UI | Author Year | Study Design* | Location (e.g., City and Country, latitude) | N enrolled*** | N analyzed | Mean (SD) Age, yr | Age Range / IQR | Male, % | Race / Ethnicity | Anthropometry data (e.g., BMI, weight, or %body fat ...etc) | Health Status | Specific Nutrition Status Data (e.g., malnourish, low Vit D or Ca intake ...etc.) |
|----|-------------|---------------|---|---------------|------------|-------------------|-----------------|---------|------------------|---|---------------|---|
| | | | | | | | | | | | | |

*Please copy from above

**Report baseline data for all subjects: preferred data for subjects actually analyzed than for subjects that enrolled in the study.

***For RCT, N enrolled is the number of subjects randomized. For cohort study, N enrolled is the total number of subjects fulfilled study inclusion criteria. For case-cohort study, please report as detailed information as possible on subjects selection. For example, original cohort sample size, number of subjects provided exposure data (eg. blood sample or dietary assessment), number of subjects had outcome data ...etc.

Background Diet*

| UI | Author Year | Exposure | Dietary Assessment Method** | Food Composition Database*** | Internal Calibration (or Validity) of Dietary Assessment? (y/n) If Yes, Provide Data | Biomarker Assay**** | Analytical Validity of Biomarker Data Reported? (y/n) If Yes, Provide Data | Time between Biomarker Sampling and Analysis | Season/Date when the biomarker samples were drawn | Background exposure data |
|----|-------------|--|-----------------------------|------------------------------|--|---------------------|--|--|---|--------------------------|
| | | 25(OH)D and/or 1,25(OH) 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 (eg quartiles) is given (ranges)? (y/n) applicable for categorical analyses only | a) Adjusted or matched for ANY confounders (other than age and sex)?** (y/n) | a) Clear definition of outcome, including time of ascertainment? (y/n) | a) Prospective collection of data? (y/n) |
| | | b) Sampling of population random or consecutive? (y/n) | b) Outcome assessor blinded to exposure measurement? (y/n) | b) Food composition database or suppl composition reported? (y/n) | Time from sample collection to sample analysis reported? (y/n) | | | b) Loss to follow-up <20%? (y/n) | b) Analysis was planned when cohort was formed? (y/n) |
| | | | | c) Internal calibration of method perform (if FFQ)? (y/n/NA) | | | | b) Justification of final adjusted model selection? (y/n) | c) Do the authors specify a primary outcome? (y/n) |
| OVERALL Grade (A/B/C): | | | | | | | | | |
| Explanation for Overall Quality Grade (if not Grade A): | | | | | | | | | |

*Check "NA" and skip all questions if study did not use dietary assessment or biomarkers

**We will judge in the end if the set of confounders is adequate

***Prespecified methods: HPLC, RIA kits, LC-MS/MS; EIA/Chemiluminescence

Appendix F. Excluded Studies

| Excluded Study | Reason |
|---|--|
| Aalberts JS, Weegels PL, van der HL et al. Calcium supplementation: effect on blood pressure and urinary mineral excretion in normotensive male 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-hydroxy Vitamin 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 or 4 study |
| Ala-Houhala M. 25-Hydroxy Vitamin 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 |

| Excluded Study | Reason |
|---|--|
| Anonymous. Vitamin D supplementation for northern native communities. Indian and Inuit Health Committee, Canadian Paediatric Society. CMAJ Canadian Medical Association Journal 138 (3):229-30, 1988. | Review paper |
| Armitage NC, Rooney PS, Gifford KA, Clarke PA, Hardcastle JD. The effect of calcium supplements on rectal mucosal proliferation. British Journal of Cancer 71 (1):186-90, 1995. | No outcomes of interest |
| Armstrong AL, Osborne J, Coupland CA, Macpherson MB, Bassey EJ, Wallace WA. Effects of hormone replacement therapy on muscle performance and balance in post-menopausal women. Clinical Science 91 (6):685 -90, 1996. | Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect |
| Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyVitamin D levels in healthy women. Journal of Clinical Endocrinology & Metabolism 88 (1):157-61, 2003. | Cross-sectional or retrospective assessment of diet after disease diagnosis |
| August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. American Journal of Obstetrics & Gynecology. 191(5):1666-72, 2004 Nov. | >=20% subjects with diseases |
| August P, Marcaccio B, Gertner JM, Druzin ML, Resnick LM, Laragh JH. Abnormal 1,25-dihydroxyVitamin D metabolism in preeclampsia. American Journal of Obstetrics & Gynecology 166 (4):1295-9, 1992. | Cross-sectional or retrospective assessment of diet after disease diagnosis |
| Back O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Dermato -Venereologica 89 (1):28 -32 , 2009. | combination of vit D/Ca and other treatment w/o analysis of independent effect |
| Bailey BW, Sullivan DK, Kirk EP, Hall S, Donnelly JE. The influence of calcium consumption on weight and fat following 9 months of exercise in men and women. Journal of the American College of Nutrition 2007; 26(4):350-355. | No outcomes of interest |
| Bakker R, Rifas-Shiman SL, Kleinman KP, Lipshultz SE, Gillman MW. Maternal calcium intake during pregnancy and blood pressure in the offspring at age 3 years: a follow-up analysis of the Project Viva cohort. American Journal of Epidemiology 168 (12):1374 -80 , 2008. | age <18 (BP outcome) |
| Baron JA, Beach M, Mandel JS et al. Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. Annals of the New York Academy of Sciences 889:138-45, 1999. | Duplicate publication (see Baron 1999 NEJM) |
| Baron JA, Beach M, Mandel JS et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. . New England Journal of Medicine 340 (2):101-7, 1999. | In Weigarten 2008 systematic review |
| Baron JA, Tosteson TD, Wargovich MJ et al. Calcium supplementation and rectal mucosal proliferation: a randomized controlled trial. . Journal of the National Cancer Institute 87 (17):1303-7, 1995. | No outcomes of interest |
| Barr SI. Calcium and body fat in peripubertal girls: cross-sectional and longitudinal observations. Obesity 2007; 15(5):1302-1310. | Not RCT growth study |
| Barsoum GH, Hendrickse C, Winslet MC et al. Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. British Journal of Surgery 79 (6):581-3, 1992. | No outcomes of interest |

| Excluded Study | Reason |
|---|---|
| Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose Vitamin D supplementation on serum Vitamin D levels and milk calcium concentration in lactating women and their infants. <i>Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine</i> 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.. <i>BMJ</i> 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.. <i>New England Journal of Medicine</i> 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. <i>JAMA</i> 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. <i>American Journal of Obstetrics & Gynecology</i> 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. <i>Journal of Clinical Investigation</i> 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. <i>Journal of Bone & Mineral Research</i> 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. <i>Journal of Bone & Mineral Research</i> 3(4):369-73, 1988. | No outcomes of interest |
| Bell NH. Hypercalcemic and hypocalcemic disorders: diagnosis and treatment. <i>Nephron</i> 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. <i>Osteoporosis International</i> 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.. <i>Archives of Pediatrics & Adolescent Medicine</i> 159 (6):543 -50, 2005. | Not RCT growth study |
| Berube S, Diorio C, Masse B et al. Vitamin D and calcium intakes from food or supplements and mammographic breast density. <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 |

| Excluded Study | Reason |
|---|---|
| Bischoff HA, Stahelin HB, Dick W et al. Effects of Vitamin D and calcium supplementation on falls: a randomized controlled trial.. Journal of Bone & Mineral Research 18 (2):343-51, 2003. | In Ottawa EPC report |
| Bischoff-Ferrari HA, Conzelmann M, Stahelin HB et al. Is fall prevention by Vitamin D mediated by a change in postural or dynamic balance? Osteoporosis International 2006; 17(5):656-663. | Secondary analysis of an original RCT by Bischoff-Ferrari 2003, which is already in Ottawa's report |
| Bischoff-Ferrari HA, Orav EJ, Wronn-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Archives of Internal Medicine 166 (4):424-30, 2006. | In Ottawa EPC report |
| Blum M, Kirsten M, Worth MH, Jr. Reversible hypertension. Caused by the hypercalcemia of hyperparathyroidism, Vitamin D toxicity, and calcium infusion. JAMA 237 (3):262 -3, 1977. | No 25(OH)D or dietary Ca |
| 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. Obstetrics & Gynecology 90 (2):157-61, 1997. | In Hofmeyer 2007 systematic review |
| Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. . Lancet 356 (9238):1300-6, 2000. | In Weigarten 2008 systematic review |
| Bonithon-Kopp C, Piard F, Fenger C et al. Colorectal adenoma characteristics as predictors of recurrence. Diseases of the Colon & Rectum 47 (3):323-33, 2004. | Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect |
| Boon N, Koppes LL, Saris WH, Van MW. The relation between calcium intake and body composition in a Dutch population: The Amsterdam Growth and Health Longitudinal Study. American Journal of Epidemiology 162 (1):27-32, 2005. | No outcomes of interest |
| Bostick RM, Fosdick L, Grandits GA, Grambsch P, Gross M, Louis TA. Effect of calcium supplementation on serum cholesterol and blood pressure. A randomized, double-blind, placebo-controlled, clinical trial. Archives of Family Medicine 9(1):31-8 2000. | >=20% subjects with diseases |
| Bostick RM, Fosdick L, Wood JR et al. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial.. Journal of the National Cancer Institute 87 (17):1307-15, 1995. | No outcomes of interest |
| Bostick RM, Potter JD, Fosdick L et al. Calcium and colorectal epithelial cell proliferation: a preliminary randomized, double-blinded, placebo-controlled clinical trial. Journal of the National Cancer Institute. 85(2):132-41, 1993 Jan 20. | No outcomes of interest |
| Boutron MC, Faivre J, Marteau P, Couillaud C, Senesse P, Quipourt V. Calcium, phosphorus, Vitamin D, dairy products and colorectal carcinogenesis: a French case--control study.. British Journal of Cancer 74 (1):145-51, 1996. | Cross-sectional or retrospective assessment of diet after disease diagnosis |

| Excluded Study | Reason |
|--|--|
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| Excluded Study | Reason |
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| 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 |
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| Excluded Study | Reason |
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| Excluded Study | Reason |
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| 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 |
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| 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 <i>Arch Dis Child</i> . 2007 Nov;92(11):1049]. <i>Archives of Disease in Childhood</i> 2007; 92(9):750-753. | Relationship between mother's 25(OH)D and infant's 25(OH)D levels |
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| Excluded Study | Reason |
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| Excluded Study | Reason |
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| 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 |
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| 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 |
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| 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 |
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| Excluded Study | Reason |
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| 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 |
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| 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 |
| 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 |
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| 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 |

| Excluded Study | Reason |
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| 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):I150-4, 1991. | Cross-sectional or retrospective assessment of diet after disease diagnosis |
| Hamid Z, Riggs A, Spencer T, Redman C, Bodenner D. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed Vitamin D.. <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 |
| Herrmann U, Schwille PO, Schmiedl A, Fan J, Manoharan M. Acute effects of calcium sodium citrate supplementation of a test meal on mineral homeostasis, oxalate, and calcium oxalate crystallization in the urine of healthy humans--preliminary results in patients with idiopathic calcium urolithiasis. <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 |

| Excluded Study | Reason |
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| 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 |
| Hintzpete 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 |
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| 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 |
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| 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 |
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| Excluded Study | Reason |
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| 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 |
| 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 |
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| 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 |

| Excluded Study | Reason |
|---|---|
| John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. . Journal of Steroid Biochemistry & Molecular Biology 89 -90 (1-5):549 -52, 2004. | No 25(OH)D or dietary Ca |
| John WG, Noonan K, Mannan N, Boucher BJ. HypoVitaminosis D is associated with reductions in serum apolipoprotein A-I but not with fasting lipids in British Bangladeshis. American Journal of Clinical Nutrition 82 (3):517-22, 2005. | Cross-sectional or retrospective assessment of diet after disease diagnosis |
| Johnson MA, Fischer JG, Park S. Vitamin D deficiency and insufficiency in the Georgia Older Americans Nutrition Program. Journal of Nutrition for the Elderly 27 (1-2):29 -46 , 2008. | combination of vit D/Ca and other treatment w/o analysis of independent effect |
| Johnson NE, Smith EL, Freudenheim JL. Effects on blood pressure of calcium supplementation of women. American Journal of Clinical Nutrition 42 (1):12-7, 1985. | In systematic review |
| Jones G, Scott F. Low bone mass in premenopausal parous women: identification and the effect of an information and bone density feedback program. . Journal of Clinical Densitometry 2(2):109-15, 1999. | No outcomes of interest |
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| 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. Am J Epidemiol 1994; 139(1):16-29. | Same cohorts as Wu 2002 RefID 529 (HPFS & NHS) and same exposure-outcome relationship but shorter follow-up |
| Karanja N, Morris CD, Illingworth DR, McCarron DA. Plasma lipids and hypertension: response to calcium supplementation. American Journal of Clinical Nutrition 45 (1):60-5, 1987. | No outcomes of interest |
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| Kearney J, Giovannucci E, Rimm EB et al. Calcium, Vitamin D, and dairy foods and the occurrence of colon cancer in men. American Journal of Epidemiology 143 (9):907-17, 1996. | Longer followup data were published in Wu 2002 |
| Kemi VE, Karkkainen MU, Karp HJ, Laitinen KA, Lamberg-Allardt CJ. Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose-response study in healthy females. British Journal of Nutrition 99 (4):832-9, 2008. | No outcomes of interest |
| Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 57 (5):M321-5, 2002. | No 25(OH)D or dietary Ca |

| Excluded Study | Reason |
|---|--|
| Kenny AM, Biskup B, Robbins B, Marcella G, Burluson JA. Effects of Vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. <i>Journal of the American Geriatrics Society</i> 51 (12):1762-7, 2003. | In Ottawa EPC report |
| Kesteloot H, Geboers J. Calcium and blood pressure. <i>Lancet</i> 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. <i>New England Journal of Medicine</i> 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. <i>International Journal of Food Sciences & Nutrition</i> 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. <i>Epidemiology</i> . 19(5):666-71, 2008 Sep. | No outcomes of interest |
| Knight KB, Keith RE. Calcium supplementation on normotensive and hypertensive pregnant women. <i>American Journal of Clinical Nutrition</i> 55 (4):891-5, 1992. | No outcomes of interest |
| Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. <i>Lancet</i> 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. <i>Biological Trace Element Research</i> 89(2):145-53, 2002. | No 25(OH)D or dietary Ca |
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| Kokot F, Pietrek J, Srokowska S et al. 25-hydroxyVitamin D in patients with essential hypertension. <i>Clinical Nephrology</i> 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. <i>Nutrition & Cancer</i> 2006; 56(1):22-30. | No outcomes of interest |
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| Kromhout D, Bosschieter EB, Coulander CD. Potassium, calcium, alcohol intake and blood pressure: the Zutphen Study. <i>American Journal of Clinical Nutrition</i> 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. <i>International Journal of Gynaecology & Obstetrics</i> 63 (3):231-46, 1998. | SR of prevention of maternal morbidity |

| Excluded Study | Reason |
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| 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 |

| Excluded Study | Reason |
|---|--|
| 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 |
| 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 |

| Excluded Study | Reason |
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| 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 |
| 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 |

| Excluded Study | Reason |
|---|---|
| Markestad T, Kolmannskog S, Arntzen E, Toftegaard L, Haneberg B, Aksnes L. Serum concentrations of Vitamin D metabolites in exclusively breast-fed infants at 70 degrees north. <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, Pepler 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, Pepler 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 |

| Excluded Study | Reason |
|---|---|
| McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension. A randomized, double-blind, placebo-controlled, crossover trial. <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, Binquet C, Boutron-Ruault MC, Paillot B, Faivre J, Bonithon-Kopp C. Dietary fatty acids and recurrence of colorectal adenomas in a European intervention trial. <i>Nutrition & Cancer</i> 60 (5):560 -7 , 2008. | no 25(OH)D or dietary Ca |
| Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci E. Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in US men. <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 |

| Excluded Study | Reason |
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| 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 |
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| 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 (postmenepausal women) |
| Nilas L, Christiansen C. Treatment with Vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. <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 |
| 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 <i>J Bone Miner Metab.</i> 2003;21(4):253]. <i>Journal of Bone & Mineral Metabolism</i> 21(2):103-8, 2003. | No outcomes of interest |
| Nishiyama T. Effects of calcium on muscular training. <i>Journal of Nutritional Science & Vitaminology</i> 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. <i>Roczniki Panstwowego Zakladu Higieny</i> 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. <i>Hypertension</i> 13(6 Pt 1):630-9, 1989. | In systematic review |
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| Excluded Study | Reason |
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| Ochner CN, Lowe MR. Self-reported changes in dietary calcium and energy intake predict weight regain following a weight loss diet in obese women. <i>Journal of Nutrition</i> 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. <i>Annals of Nutrition & Metabolism</i> 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. <i>Acta Paediatrica</i> 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. <i>Puerto Rico Health Sciences Journal</i> 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. <i>Pediatric Dermatology</i> 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. <i>Nephrology Dialysis Transplantation</i> 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. <i>Turkish Journal of Pediatrics</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 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. <i>Annals of Internal Medicine</i> 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. . <i>International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity</i> 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. <i>Stroke</i> 39 (9):2611-3, 2008. | >=20% subjects with diseases |
| Pilz S, Dobnig H, Winklhofer-Roob B et al. Low serum levels of 25-hydroxyVitamin D predict fatal cancer in patients referred to coronary angiography. <i>Cancer Epidemiology, Biomarkers & Prevention</i> 17(5):1228-33, 2008. | >=20% subjects with diseases |
| Pittard WB, III, Geddes KM, Hulsey TC, Hollis BW. How much Vitamin D for neonates? <i>American Journal of Diseases of Children</i> 145 (10):1147-9, 1991. | Not RCT arrow 4 study |

| Excluded Study | Reason |
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| Pittard WB, III, Geddes KM, Sutherland SE, Miller MC, Hollis BW. Longitudinal changes in the bone mineral content of term and premature infants. . American Journal of Diseases of Children 1990; 144(1):36-40. | Changes in 25(OH)D status of term and premature infants |
| Pittas AG, Harris SS, Stark PC, wson-Hughes B. The effects of calcium and Vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults.. Diabetes Care 2007; 30(4):980-986. | No outcomes of interest |
| Porojnicu AC, Robsahm TE, Dahlback A et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer 2007; 55(3):263-270. | Ecological study |
| Prentice A, Ginty F, Stear SJ, Jones SC, Laskey MA, Cole TJ. Calcium supplementation increases stature and bone mineral mass of 16- to 18-year-old boys. Journal of Clinical Endocrinology & Metabolism 90 (6):3153-61, 2005. | In Winzenberg 2007 systematic review |
| Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiology 8 (1):31-6, 1997. | No outcomes of interest |
| Purwar M, Kulkarni H, Motghare V, Dhole S. Calcium supplementation and prevention of pregnancy induced hypertension. Journal of Obstetrics & Gynaecology Research 22 (5):425-30, 1996. | In Hofmeyer 2007 systematic review |
| Rajalakshmi R, Sail SS, Shah DG, Ambady SK. The effects of supplements varying in carotene and calcium content on the physical, biochemical and skeletal status of preschool children. British Journal of Nutrition 30 (1):77-86, 1973. | Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect |
| Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. American Journal of Clinical Nutrition 83 (3):559-66, 2006. | No outcomes of interest |
| Rees GA, Doyle W, Srivastava A, Brooke ZM, Crawford MA, Costeloe KL. The nutrient intakes of mothers of low birth weight babies - a comparison of ethnic groups in East London, UK. Maternal & Child Nutrition 1(2):91-9, 2005. | No outcomes of interest |
| Repke JT, Villar J, Anderson C, Pareja G, Dubin N, Belizan JM. Biochemical changes associated with blood pressure reduction induced by calcium supplementation during pregnancy. American Journal of Obstetrics & Gynecology 160 (3):684-90, 1989. | In Hofmeyer 2007 systematic review |
| Repke JT, Villar J. Pregnancy-induced hypertension and low birth weight: the role of calcium. American Journal of Clinical Nutrition 1991; 54(1:Suppl): Suppl-241S. | Review paper |
| Resnick LM, Oparil S, Chait A et al. Factors affecting blood pressure responses to diet: the Vanguard study. American Journal of Hypertension 13(9):956-65, 2000. | Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect |
| Reunanen A, Knekt P, Marniemi J, Maki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. European Journal of Clinical Nutrition 50 (7):431-7, 1996. | No 25(OH)D or dietary Ca |
| Rich GM, McCullough M, Olmedo A, Malarick C, Moore TJ. Blood pressure and renal blood flow responses to dietary calcium and sodium intake in humans. American Journal of Hypertension 4(11):642S-645S, 1991. | Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect |

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| 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 |
| 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 |

| Excluded Study | Reason |
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| 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 |
| 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 |

| Excluded Study | Reason |
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| 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 |

| Excluded Study | Reason |
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| 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 |
| 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 |

| Excluded Study | Reason |
|---|--|
| Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm 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 |
| TwoRoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyVitamin D and 1,25-dihydroxyVitamin D and risk of incident ovarian cancer. <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 |
| 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 |
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