# Vitamin D and Calcium: A Systematic Review of Health Outcomes

Tufts Evidence-based Practice Center

August 4, 2009

Information Gathering Workshop
Committee to Review DRI for Vitamin D and Calcium

# Topics to be Discussed

- Background of this report
- AHRQ EPC evidence report process
- Brief descriptions of methods
  - Key questions and analytic framework
  - Selection criteria
  - Literature search
  - Critical appraisal of evidence
  - Reporting of evidence
- Overview of available evidence
- Illustration of reporting of one outcome
- Closing remarks

# Sponsors of this Report

- Office of Dietary Supplements, NIH
- Centre for Chronic Disease Prevention and Control, Public Health Agency of Canada
- Office of Nutrition Policy and Promotion, Health Canada
- Food and Drug Administration, DHHS

# Tufts EPC Staff

Mei Chung, MPH (PhD candidate) *
Ethan M Balk, MD, MPH *
Michael Brendel, BA
Stanley Ip, MD
Joseph Lau, MD *
Jounghee Lee, PhD *
Alice Lichtenstein, DSc
Kamal Patel, MBA, MPH
Gowri Raman, MD
Athina Tatsioni, MD, PhD
Teruhiko Terasawa, MD
Thomas A Trikalinos, MD, PhD *

* present at this meeting

# Conflict of Interest Declaration

No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in this report.

# Technical Expert Panel

meeting 9/20/2008

Steven Abrams, MD *

Stephanie Atkinson, PhD

Patsy M. Brannon, PhD *

Rebecca D. Jackson, PhD

Glennville Jones, PhD *

Susan Taylor Mayne, PhD *

Clifford J. Rosen, MD *

* DRI committee member

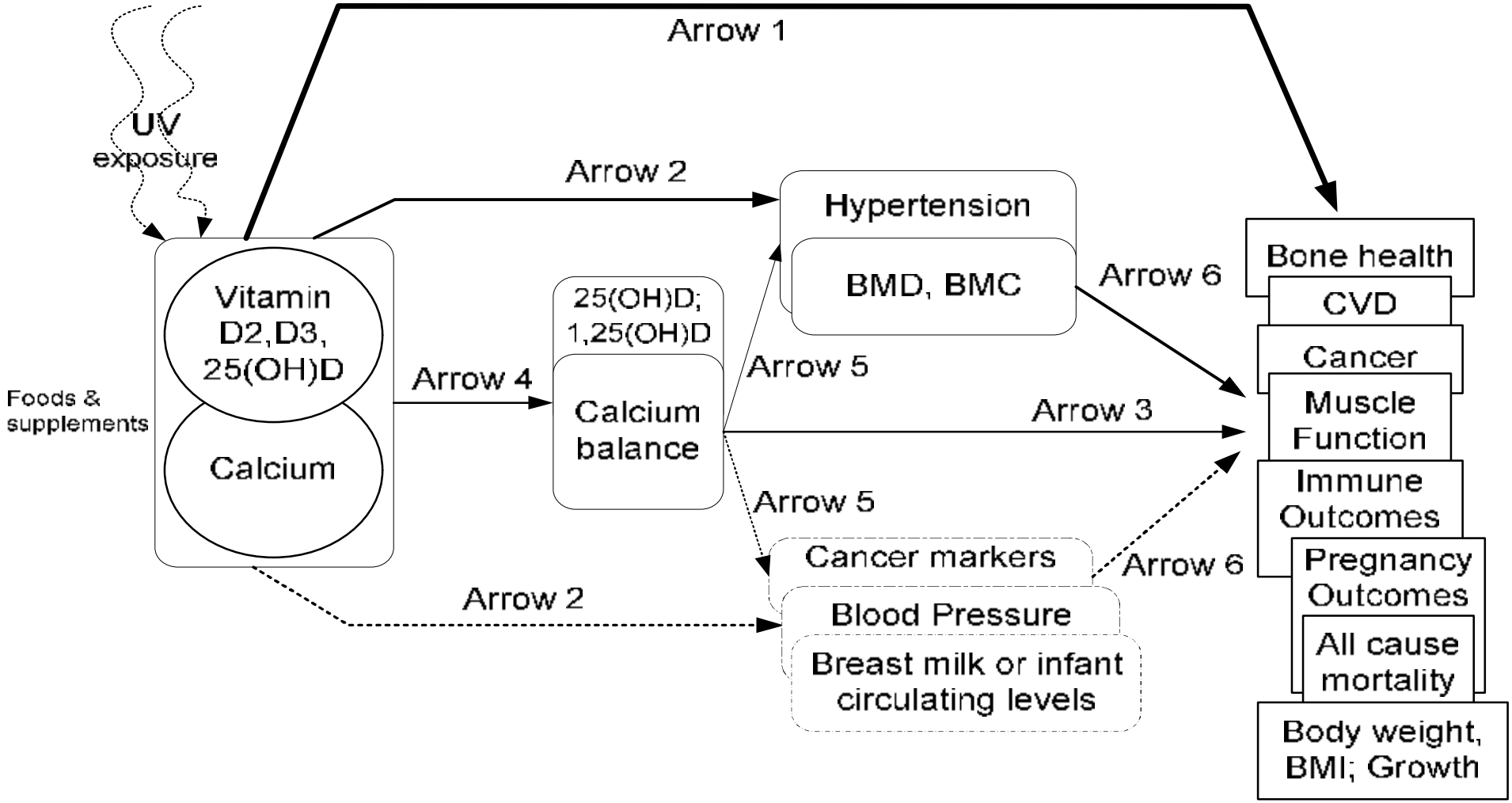
# AHRQ Evidence Report Process

- Form Technical Expert Panel
- Refine key questions, define selection criteria
- Perform literature search
- Screen abstracts for potentially relevant articles
- Retrieve full text articles of screened in abstracts
- Select articles according to criteria
- Extract data from articles that meet inclusion criteria
- Critically appraise studies (methodological quality, applicability)
- Create evidence and summary tables
- Synthesize results
- Perform meta-analysis as appropriate
- Draft report
- Send out for peer review, perform update and revise report
- 12-month process
- ***Report provides information for decision makers, it does not make clinical or policy recommendations***

# Analytic Framework

- Relevant questions can be formulated into a model that analyzes all effects and interactions between intervention or exposure and outcomes; to appreciate relationships of the questions
- Can be used to clarify and generate questions (topics)
- Can highlight what aspects are known and unknown
- Can clarify what study designs may be best to address specific questions

# Analytic Framework for Vitamin D and/or Calcium Health Outcomes



# Key Questions of Vitamin D and Calcium Report

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)

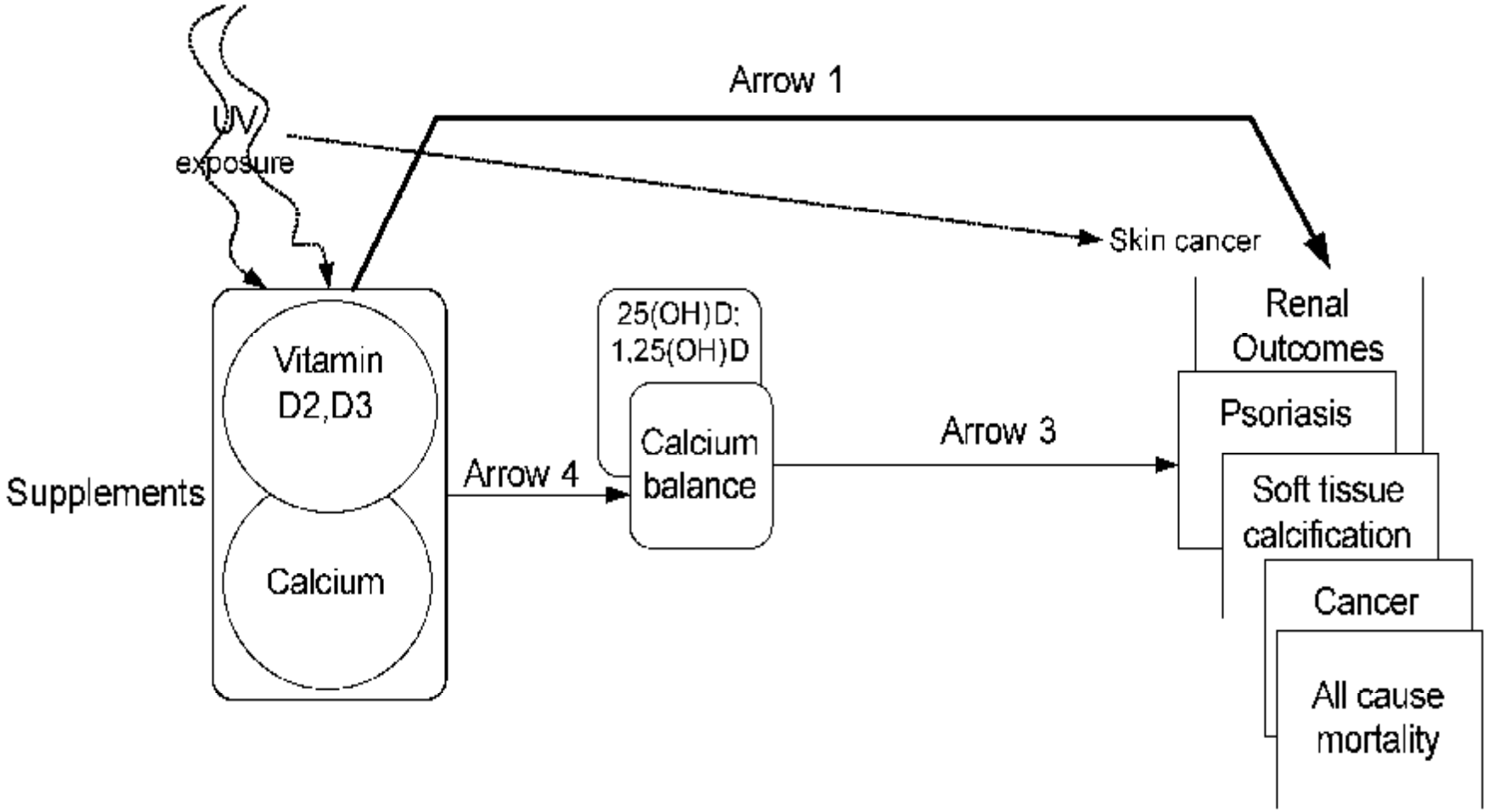
Key Question 2. What is the effect of vitamin D, calcium or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density? (Arrow 2)

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)

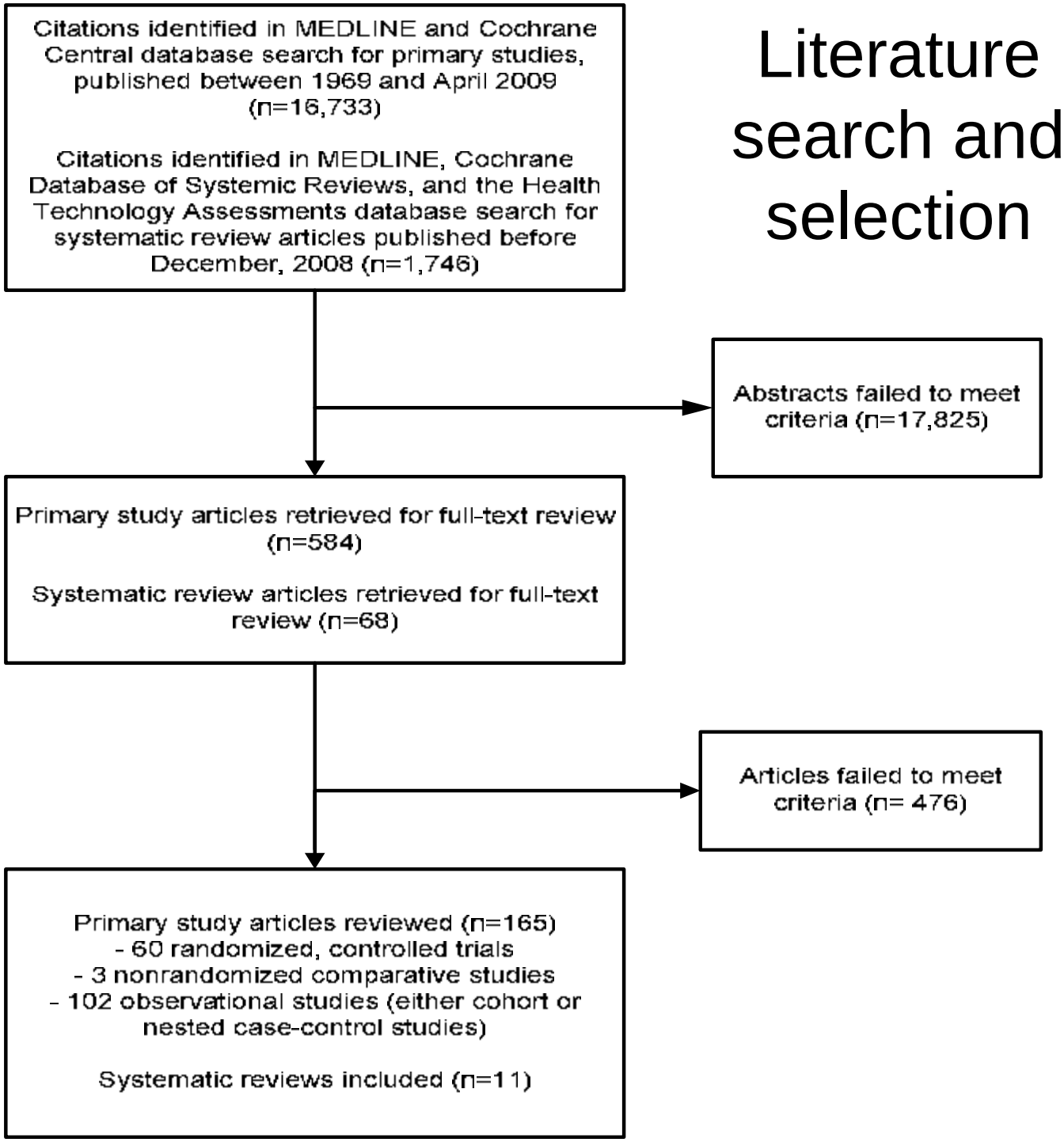
# Analytic Framework for Vitamin D and/or Calcium Safety-related (adverse) Outcomes



# PICO Selection Criteria
(partial list)

- **P**opulation
  - Generally healthy people with no known disorders
  - Studies enrolled <20% patients with common diseases
  - Any population for adverse effects of high intake
- **I**ntervention / **E**xposure
  - Calcium intake, Vitamin D intake, or both
  - Observational studies: Serum 25(OH)D measurement
- **C**omparator
  - Dose relationship
- **O**utcome
  - 17 outcomes selected by technical expert panel
- **S**tudy Design
  - Experimental or observational, study duration
  - Excluded cross-sectional studies and studies that did not prospectively collect Vitamin D measurements before the outcome

# Literature search and selection



# Critical Appraisal of Primary Studies

We adapted a 3-category grading system of the *AHRQ Methods Reference Guide for Comparative Effectiveness Reviews*, which encompasses the principles of CONSORT statement for RCTs, STROBE checklist for observational studies. This system defines a generic grading system that is applicable to each type of study design.

**A** - Least bias; results are valid

**B** - Susceptible to some bias, but not sufficient to invalidate the results

**C** - Significant bias that may invalidate the results

# Critical Appraisal of Systematic Reviews

- A summary quality grade for systematic review is difficult to interpret
- Various dimensions and nuances of the systematic review must be understood
- We applied AMSTAR checklist, a tool to assess the quality of reporting of systematic reviews
- Items evaluated are made explicit for the reader
- Comments provided where appropriate

# Critical Appraisal of Systematic Reviews
## (example of AMSTAR application)

| | |
|---|---|
| **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<br>Calcium supplement: WMD = -1.79 (-3.04, -0.55)[C], statistically homogeneous<br>Dairy supplementation: WMD = +0.85 (-4.39, +6.08), statistically heterogeneous<br>ANCOVA, adjusting for baseline weight:<br>Calcium: Effect = -0.41 (-1.07, +0.25) kg<br>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. | |

# Reporting of Evidence

- Evidence tables
  - detailed information about each study
- Summary tables
  - summary from each study that addresses a question (outcome, study design)
- Figures, graphs
- Meta-analyses (if appropriate)
- Narratives, highlight features and limitation of study in answering question

# Results

# Primary Studies on Vitamin D Intake or Concentration

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

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

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

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

# Availability and Quality of Primary Studies

| | Quality grade of primary studies | | |
|---|---|---|---|
| | **A (11%)** | **B (50%)** | **C (39%)** |
| **Vitamin D (94)** | | | |
| **RCT (30)** | 3 | 14 | 13 |
| **Non-RCT (64)** | 4 | 33 | 27 |
| **Calcium (108)** | | | |
| **RCT (23)** | 1 | 11 | 11 |
| **Non-RCT (85)** | 17 | 41 | 27 |
| **Vitamin D + Calcium (19)** | | | |
| **RCT (19)** | 0 | 12 | 7 |
| **Non-RCT (0)** | 0 | 0 | 0 |

Total = 221 (from 165 unique studies); same study may contribute more than one outcome

# Organization of Results Chapter

- Vitamin D
  - outcomes
- Calcium
  - outcomes
- Vitamin D + calcium
  - Outcomes
- Association with intake and serum Vitamin D level (Question 4)
- Adverse or Safety Outcomes

# Reporting of Individual Outcomes

- Synopsis
- Detailed presentation (highlight features and limitation of study in answering question)
  - Findings per vitamin D concentration
  - Findings per age and sex
  - Findings by life stage
- Summary tables
  - RCTs
    - Characteristics
    - Results
  - Cohort studies
    - Characteristics
    - Results
- Figures, graphs
- Meta-analyses (if appropriate)

## Colorectal cancer

*Synopsis*

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

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

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

*Findings 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 negative trend between 25(OH)D concentrations and 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 a negative trend in colon cancer risk and rectal cancer risk, 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 negative trend between 25(OH)D concentrations and colorectal cancer risk was found in these two studies.
- **Pregnant & lactating women** Not reviewed

# Vitamin D and colorectal cancer: results of RCTs (pg 68)

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

| Author Year Study Name Location (Latitude) [PMID] | Population | | Background Calcium Intake & Vitamin D Data | Comparisons | Compliance | Comments |
|---|---|---|---|---|---|---|
| Trivedi 2003[44] Oxford, UK (52°N) [12609940] | • Health status<br>• Mean age (range), y<br>• Male (%) | General population<br>75 (65-85)<br><br>76% | 25(OH)D: 53.4 nmol/L<br><br>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.

# Vitamin D and colorectal cancer: results of RCTs (pg 70)

**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 | | | | | |

# Vitamin D and colorectal cancer – observational studies (pg 74)

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

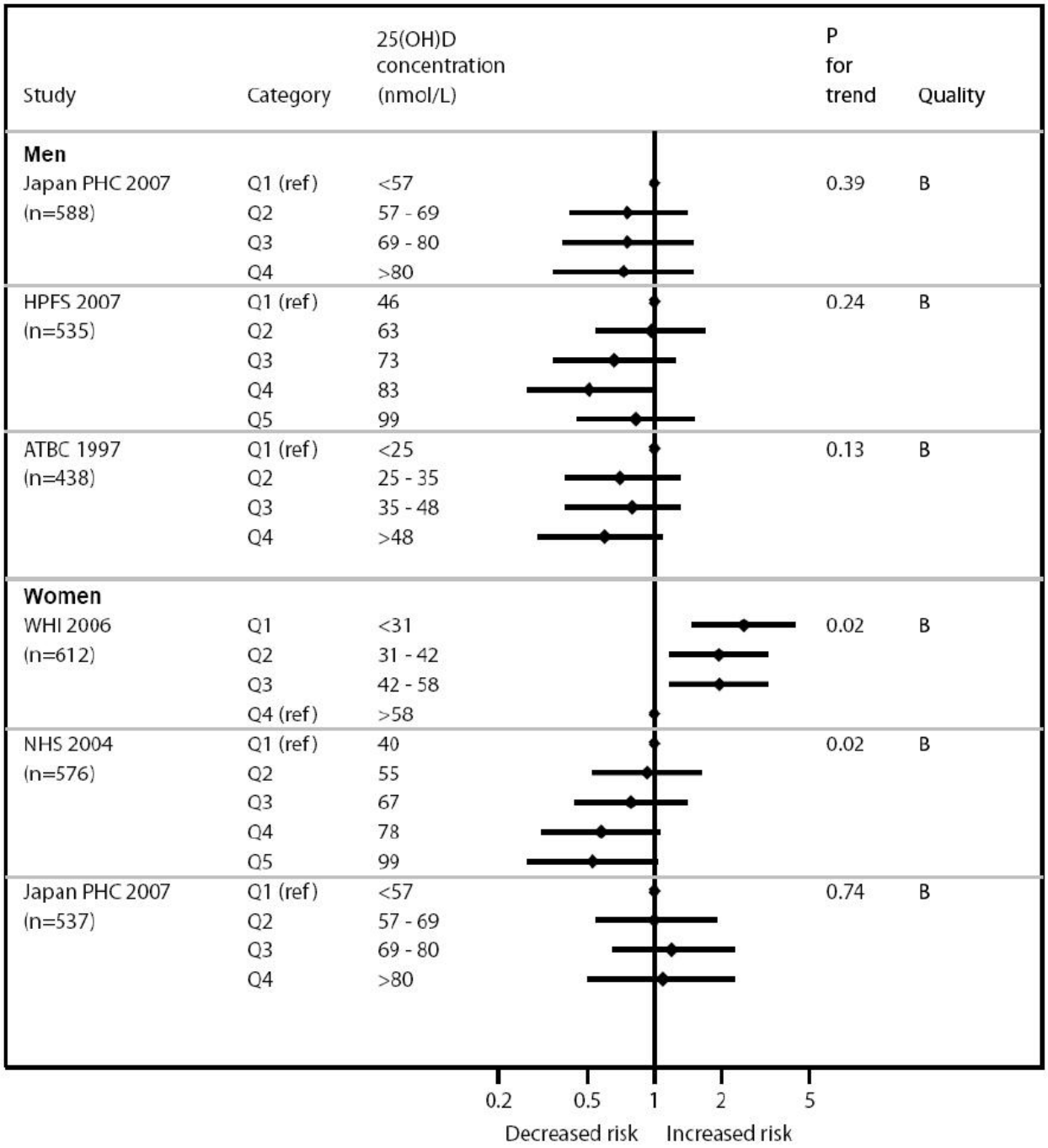
| Author Year Study Name Location (Latitude) [PMID] | Population | | Vitamin D Concentration | | Comparisons | Confounders/Effect Modifiers Adjusted | | | | | | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Nutrients | Demograph | Anthrop | Medical | UV exposure | Lifestyle | |
| **Cohort** | | | | | | | | | | | | |
| Freedman 2007[53] NHANES III US (various) [16481636] | • Health status<br>• Mean age (range), y<br>• Male (%) | Any<br>44 (≥17)<br>45 | • Assay method<br>• Season blood drawn | RIA (DiaSorin)<br>All | Colorectal cancer mortality stratified by prespecified baseline 25(OH)D cut points | X | X | X | X | X | X | White: 71%; Black: 14%; Hispanic: 6%; Others: 9% |
| **Nested case-control** | | | | | | | | | | | | |
| Braun 1995[73] WCC Maryland, US (38°N) [329893] | • Health status<br>• Mean age (range), y<br>• Male (%) | Any<br>55 (nd)<br>nd | • Assay method<br>• Season blood drawn | RIA (Horris 1993)<br>Fall | • 25(OH)D levels between cases and controls<br>• Colon cancer risk stratified by baseline 25(OH)D quintiles | | X | | | X | | |

# Vitamin D and colorectal cancer: Results of observational studies (pg 76)

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

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

**Figure 8. Colorectal cancer risk stratified by vitamin D concentration**



# Caveats

- WYSWYA - report provides information only on questions formulated *a priori*, it does not answer all potential questions of interest
- As much as we strive to be objective, some judgment is inevitable (e.g., grading of studies)
- No standard tool available to assess quality of nutritional observational studies
- Publication bias
- Need to rely on existing systematic reviews, but using them is challenging
- Studies in general were not designed for DRI issues (e.g., targeting DRI life stages)
- Evidence report is meant to inform, not replace decision making by expert bodies