**APPENDICE**S

1. Documentation of vitamin D search

2. Evidence tables

3. Summary tables

4. List of excluded studies

**Appendix 1.** Documentation of vitamin D search

## Vitamin D, research question 1

**What is the effect of vitamin D from different sources on serum 25-OHD concentrations?**

(“Calcifediol"[MH] OR "25-hydroxycholecalciferol"[ALL] OR "25-hydroxyvitamin D"[ALL] OR 25-OH\*[ALL] OR "25(OH)D"[ALL] OR "64719-49-9"[RN] OR "19356-17-3"[RN] OR "vitamin D status"[TIAB] OR "vitamin D level"[TIAB] OR "vitamin D concentration"[TIAB] OR "plasma vitamin D"[TIAB] OR "serum vitamin D"[TIAB]) AND ("Food and Beverages"[MH] OR "Diet"[MH] OR "Diet Therapy"[MH] OR "Eating"[MH] OR "Sunlight"[MH] OR "Seasons"[MH] OR "diet" [TIAB] OR "diet"[TIAB] OR "dieting"[TIAB] OR "food"[TIAB] OR nutriti\*[TIAB] OR ultraviolet\*[TIAB] OR "sun"[TIAB] OR "sunlight"[TIAB] OR "sunny"[TIAB] OR supplement\* [TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "randomized controlled"[ALL] OR "randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[mesh]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 2

**What is the relationship between 25-OHD concentrations and different outcomes in different population and age groups?**

("Calcifediol"[MH] OR "64719-49-9"[RN] OR "19356-17-3"[RN] OR "25-hydroxycholecalciferol"[ALL] OR "25-hydroxyvitamin D"[ALL] OR "25-OHD"[ALL] OR "25(OH)D"[ALL] OR (25(OH)D[ALL]) OR "vitamin D status"[TIAB] OR "vitamin D level"[TIAB] OR "vitamin D concentration"[TIAB] OR "plasma vitamin D" [TIAB] OR "serum vitamin D" [TIAB]) AND ("Pregnancy"[MH] OR "Child Development"[MH] OR "Growth"[MH] OR "Bone and Bones"[MH] OR "Bone Development"[MH] OR "Fractures, Bone"[MH] OR "Bone Density"[MH] OR "Osteoporosis"[MH] OR "Osteomalacia"[MH] OR "Rickets"[MH] OR "Oral Health"[MH] OR "Tooth"[MH] OR "Muscle Strength"[MH] OR "Accidental Falls"[MH] OR "Neoplasms"[MH] OR "Autoimmunity"[MH] OR "Autoimmune Diseases"[MH] OR "Diabetes Mellitus, Type 2"[MH] OR "Diabetes Mellitus, Type 1"[MH] OR "Metabolic Syndrome X"[MH] OR "Multiple Sclerosis"[MH] OR "Overweight"[MH] OR "Mortality"[MH] OR "mortality" [Subheading] OR "Blood Pressure"[MH] OR "Cardiovascular Diseases"[MH] OR "Infection"[MH] OR "bone quality"[TIAB] OR "bone mineral content"[TIAB] OR "bone health"[TIAB] OR "bone mass"[TIAB] OR osteopor\*[TIAB] OR autoimmun\* [TIAB] OR diabet\*[TIAB] OR obes\*[TIAB] OR "overweight"[TIAB] OR cancer\*[TIAB] OR "tumor"[TIAB] OR "tumors"[TIAB] OR tumour\* [TIAB] OR "falling"[TIAB] OR "falls"[TIAB] OR "Fall"[TIAB] OR "faller"[TIAB] OR "faller" [TIAB] OR "hypertension"[TIAB] OR infecti\*[TIAB] OR infecte\*[TIAB] OR pregnan\*[TIAB] OR gestation\*[TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "randomized controlled"[ALL] OR "randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[mesh]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research questions 3 and 4

**What is the effect of dietary vitamin D/ supplemental vitamin D/ intake on different outcomes in different population and age groups?**

( (("Vitamin D"[MH] OR "Vitamin D" [TIAB]) AND ("food"[TIAB] OR "Diet"[TIAB] OR "dieting"[TIAB] OR "Diets"[TIAB] OR "dietary"[TIAB] OR nutriti\* [TIAB] OR "Dietary Supplements"[MH] OR "Food and Beverages"[MH] OR "Diet"[MH])) OR ("supplemental vitamin D"[TIAB] OR "vitamin D supplement"[TIAB] OR "vitamin D supplements"[TIAB] OR "dietary vitamin D"[TIAB] OR "vitamin D intake”[TIAB] OR "vitamin D/administration and dosage"[MH]) ) AND ("Pregnancy"[MH] OR "Child Development"[MH] OR "Growth"[MH] OR pregnan\* [TIAB] OR gestation\* [TIAB] OR "Bone and Bones"[MH] OR "Bone Development"[MH] OR "Fractures, Bone"[MH] OR "Bone Density"[MH] OR "Osteoporosis"[MH] OR "Osteomalacia"[MH] OR "Rickets"[MH] OR "Oral Health"[MH] OR "Tooth"[MH] OR "Muscle Strength"[MH] OR "Accidental Falls"[MH] OR "Neoplasms"[MH] OR "Autoimmunity"[MH] OR "Autoimmune Diseases"[MH] OR "Diabetes Mellitus, Type 2"[MH] OR "Diabetes Mellitus, Type 1"[MH] OR "Metabolic Syndrome X"[MH] OR "Multiple Sclerosis"[MH] OR "Overweight"[MH] OR "Mortality"[MH] OR "mortality"[Subheading] OR "Blood Pressure"[MH] OR "Cardiovascular Diseases"[MH] OR "Infection"[MH] OR "bone quality" [TIAB] OR "bone mineral content" [TIAB] OR "bone health" [TIAB] OR "bone mass" [TIAB] OR osteopor\*[TIAB] OR autoimmun\*[TIAB] OR diabet\* [TIAB] OR obes\* [TIAB] OR "overweight"[TIAB] OR cancer\* [TIAB] OR "tumor"[TIAB] OR "Tumors"[TIAB] OR tumour\*[TIAB] OR "falling"[TIAB] OR "falls"[TIAB]OR "Fall"[TIAB] OR "faller"[TIAB] OR "Fallers"[TIAB] OR "Hypertension"[TIAB] OR infecti\* [TIAB] OR infecte\* [TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "Randomized controlled"[ALL] OR "Randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 5

**What is the effect of sun or UVB exposure on different outcomes in different population and age groups?**

("Sunlight"[MH] OR "Ultraviolet Therapy"[MH] OR "ultraviolet radiation" [TIAB] OR "ultraviolet ray" [TIAB] OR "ultraviolet rays" [TIAB] OR "sun"[TIAB] OR "sunny"[TIAB] OR "sunlight"[TIAB] OR UVB\* [TIAB] OR "ultraviolet light" [TIAB]) AND ("Pregnancy"[MH] OR "Child Development"[MH] OR "Growth"[MH] OR "Oral Health"[MH] OR "Tooth"[MH] OR "Muscle Strength"[MH] OR "Accidental Falls"[MH] OR "Neoplasms"[MH] OR "Autoimmunity"[MH] OR "Autoimmune Diseases"[MH] OR "Diabetes Mellitus, Type 2"[MH] OR "Diabetes Mellitus, Type 1"[MH] OR "Metabolic Syndrome X"[MH] OR "Multiple Sclerosis"[MH] OR "Overweight"[MH] OR "Mortality"[MH] OR "mortality"[Subheading] OR "Blood Pressure"[MH] OR "Cardiovascular Diseases"[MH] OR "Infection"[MH] OR "Inflammation"[MH] OR "Bone and Bones"[MH] OR "Bone Development"[MH] OR "Fractures, Bone"[MH] OR "Bone Density"[MH] OR "Osteoporosis"[MH] OR "Osteomalacia"[MH] OR "Rickets"[MH] OR pregnan\* [TIAB] OR gestation\* [TIAB] OR "bone mineral content" [TIAB] OR "bone health" [TIAB] OR "bone mass" [TIAB] OR "bone quality" [TIAB] OR osteopor\* [TIAB] OR "falling"[TIAB] OR "falls"[TIAB] OR "fall"[TIAB] OR "faller"[TIAB] OR "Fallers"[TIAB] OR cancer\* [TIAB] OR "tumor"[TIAB] OR "tumors"[TIAB] OR tumour\* [TIAB] OR autoimmun\* [TIAB] OR diabet\* [TIAB] OR obes\* [TIAB] OR "overweight"[TIAB] OR hypertens\* [TIAB] OR infecte\*[TIAB] OR infecti\*[TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "Randomized controlled"[ALL] OR "Randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 6

**Which is the UL (Tolerable Upper Intake Level) for vitamin D for different health outcomes in different population and age groups?**

( ("vitamin d/administration and dosage"[MH]) OR (("Vitamin D"[MH] OR "vitamin D" [TIAB] ) AND ("Maximum Tolerated Dose"[MH] OR "Dose-Response Relationship, Drug"[MH] OR "No-Observed-Adverse-Effect Level"[MH] OR "Risk Assessment"[MH] OR "Safety"[MH] OR "tolerable upper intake level"[TIAB] OR "UL"[TIAB] OR "tolerable dose"[TIAB] OR "tolerable doses"[TIAB] OR "tolerated dose"[TIAB] OR "tolerated doses"[TIAB] OR "upper safe limits of consumption"[TIAB] OR "upper safe limit of consumption"[TIAB] )) ) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "Randomized controlled"[ALL] OR "Randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 6 – adverse effects

("Vitamin D/adverse effects"[MH] OR "Vitamin D/agonists"[MH] OR "Vitamin D/poisoning"[MH] OR "Vitamin D/toxicity"[MH]) AND ("Randomized Controlled Trial"[ALL]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 7

**Which are the interactions of vitamin D with calcium intake on different health outcomes in different population and age groups?**

("vitamin D" [TIAB] OR "D vitamin"[TIAB] OR "D vitamins"[TIAB] OR "D-vitamin"[TIAB] OR "D-vitamins"[TIAB] OR "Vitamin D"[MH]) AND ("dietary calcium"[TIAB] OR "nutritional calcium"[TIAB] OR "supplemental calcium"[TIAB] OR "Calcium supplementation"[TIAB] OR "Calcium supplementations"[TIAB] OR "Ca supplementation"[TIAB] OR "Ca supplementations"[TIAB] OR "Ca supplements"[TIAB] OR "Ca supplement"[TIAB] OR "calcium supplement"[TIAB] OR "calcium supplements"[TIAB] OR "Calcium, Dietary"[MH] OR "Calcium Carbonate"[MH] OR "Calcium Citrate"[MH] OR "Calcium Chloride"[MH] OR "Calcium Phosphates"[MH]) AND ("Pregnancy"[MH] OR "Child Development"[MH] OR "Growth"[MH] OR "Oral Health"[MH] OR "Tooth"[MH] OR "Muscle Strength"[MH] OR "Accidental Falls"[MH] OR "Neoplasms"[MH] OR "Autoimmunity"[MH] OR "Autoimmune Diseases"[MH] OR "Diabetes Mellitus, Type 2"[MH] OR "Diabetes Mellitus, Type 1"[MH] OR "Metabolic Syndrome X"[MH] OR "Multiple Sclerosis"[MH] OR "Overweight"[MH] OR "Mortality"[MH] OR "mortality"[SH] OR "Blood Pressure"[MH] OR "Cardiovascular Diseases"[MH] OR "Infection"[MH] OR "Inflammation"[MH] OR "Bone and Bones"[MH] OR "Bone Development"[MH] OR "Fractures, Bone"[MH] OR "Bone Density"[MH] OR "Osteoporosis"[MH] OR "Osteomalacia"[MH] OR "Rickets"[MH] OR pregnan\* [TIAB] OR gestation\* [TIAB] OR "bone mineral content"[TIAB] OR "bone health"[TIAB] OR "bone mass"[TIAB] OR "bone quality"[TIAB] OR osteopor\* [TIAB] OR "falling"[TIAB] OR "falls"[TIAB] OR "fall"[TIAB OR "faller"[TIAB] OR "fallers"[TIAB] OR cancer\* [TIAB] OR "tumor"[TIAB] OR "Tumors"[TIAB] OR tumour\* [TIAB] OR autoimmun\* [TIAB] OR diabet\* [TIAB] OR obes\* [TIAB] OR "overweight"[TIAB] OR hypertens\* [TIAB] OR infecte\* [TIAB] OR infecti\* [TIAB]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## Vitamin D, research question 8

**Which is the interaction of vitamin D intake or vitamin D status with vitamin A intake or vitamin A status on health outcomes in different population and age groups?**

("Vitamin D"[MH] OR "vitamin D"[TIAB] OR "D vitamin"[TIAB] OR "D vitamins"[TIAB] OR "D-vitamin"[TIAB] OR "D-vitamins"[TIAB]) AND ("Vitamin A"[MH] OR "vitamin A"[TIAB] OR "A vitamin"[TIAB] OR "A vitamins"[TIAB] OR "A- vitamin"[TIAB] OR "A-vitamins"[TIAB]) AND ("Pregnancy"[MH] OR "Child Development"[MH] OR "Growth"[MH] OR "Oral Health"[MH] OR "Tooth"[MH] OR "Muscle Strength"[MH] OR "Accidental Falls"[MH] OR "Neoplasms"[MH] OR "Autoimmunity"[MH] OR "Autoimmune Diseases"[MH] OR "Diabetes Mellitus, Type 2"[MH] OR "Diabetes Mellitus, Type 1"[MH] OR "Metabolic Syndrome X"[MH] OR "Multiple Sclerosis"[MH] OR "Overweight"[MH] OR "Mortality"[MH] OR "mortality"[SH] OR "Blood Pressure"[MH] OR "Cardiovascular Diseases"[MH] OR "Infection"[MH] OR "Inflammation"[MH] OR "Bone and Bones"[MH] OR "Bone Development"[MH] OR "Fractures, Bone"[MH] OR "Bone Density"[MH] OR "Osteoporosis"[MH] OR "Osteomalacia"[MH] OR "Rickets"[MH] OR pregnan\*[TIAB] OR gestation\*[TIAB] OR "bone mineral content"[TIAB] OR "bone health"[TIAB] OR "bone mass"[TIAB] OR "bone quality"[TIAB] OR osteopor\*[TIAB] OR "Falling"[TIAB] OR "Falls"[TIAB] OR "Fall"[TIAB] OR "faller"[TIAB] OR "Fallers"[TIAB] OR cancer\* [TIAB] OR "tumor"[TIAB] OR "tumors"[TIAB] OR tumour\*[TIAB] OR autoimmun\*[TIAB] OR diabet\*[TIAB] OR obes\*[TIAB] OR "overweight"[TIAB] OR hypertens\*[TIAB] OR infecte\*[TIAB] OR infecti\*[TIAB]) AND ("Randomized Controlled Trial"[PT] OR "Randomized Controlled Trials as Topic"[MH] OR "Cohort Studies"[MH] OR "Intervention Studies"[MH] OR "Meta-Analysis"[PT] OR "Meta-Analysis as Topic"[MH] OR "Review"[PT] OR "Review Literature as Topic"[MH] OR "Randomized controlled"[ALL] OR "Randomised controlled"[ALL] OR "meta-analysis"[ALL] OR review\*[ALL]) AND ("humans"[MH]) AND ("2000/01/01"[PDAT] : "2011/02/28"[PDAT])

## RQ9 - Systematic reviews

("vitamin D"[TIAB] OR "D vitamin"[TIAB] OR "D vitamins"[TIAB] OR "Vitamin D"[Mesh] OR "Vitamin D Deficiency”[MH]) AND (“systematic review”[ALL] OR “systematic reviews”[ALL] OR "meta-analysis"[PT] OR “Cochrane database syst rev”[ALL]) AND (“2000/05/01” [PDAT]: “2010/10/31”[PDAT])

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| RANDOMIZED CONTROLLED TRIALS | | | |  |  |  |  |  |  |  |  |
| **Author Year Journal /Source** | **Study design** | **Summary of the study quality (A, B or C). D=excluded** | **Research question clearly formulated?** | **Design suited to test the hypothesis?** | Duration suited to test the hypothesis? | Sample size and power calculation reported /considered? | **Population well described and relevant?** | Sample recruited in an acceptable way? | Criteria for inclusion /exclusion OK? | Participants comparable with target population? | **Blinded or double-blinded?** |
| Avenell, A., et al. (2009).(56) | RCT | **C** | yes | yes, but prespecified secondary endpoint | yes | na | yes | yes | yes | yes | Double-blinded |
| Jorde, R., et al. (2010). (61) | RCT | **C** | Yes, but not primary endpoint | can't tell | yes | na | yes | yes | yes | can't tell | Double-blindet |
| Molgaard, C., et al. (2010). (40) | RCT, double blind, placebo controlled, | B | yes | yes | yes | Not reported | yes | yes | yes | yes | double-blinded |
| Urashima, M., et al. (2010).(66) | Randomiced, double blind placebo controlled trial | B | YES | YES | No | yes | yes | yes | yes | can't tell | double blind |

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| **Author Year Journal /Source** | Groups comparable with regard to factors possibly affecting the outcome? | Compliance reported and acceptable? | Drop-out rate OK? 6mo<20%, 12mo<40%, 24mo<50% | The drop-outs did not differ from the partipants? | **Intervention diets clearly defined and characterised?** | Dietary assessment method valid or validated? | Intervention diets relevant to research question? | Measurement errors of dietary reporting considered? | **Energy intake at a credible level? Results adjusted for energy?** | Food composition database reported? | **Definition of outcome /endpoint clear and OK?** | **Biological mechanism for endpoint plausible?** | Results analysed blind? |
| Avenell, A., et al. (2009).(56) | yes | yes | yes | can't tell | na | na | na | na | na | na | no | yes | can't tell |
| Jorde, R., et al. (2010). (61) | yes | yes | yes | no | na | na | na | na | na | na | yes | yes | can't tell |
| Molgaard, C., et al. (2010). (40) | yes | yes | yes | not reported | yes | Not reported | yes | not reported | na | not reported | yes | yes | not reported |
| Urashima, M., et al. (2010).(66) | yes | yes | yes | don't know | yes | NO/NA | yes | NO/NA | NO/NA | NO/NA | yes | yes | yes |

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| **Author Year Journal /Source** | In statistical analysis imbalances regarding possible confounding in groups taken into account? | Valid biomarkers used to study compliance with dietary exposure? | Possible use of medication /supplements taken into account? | Between measurement variation minimised /standardised? | Smallest effect clinically relevant /reasonable? | No possible conflicts of interest affecting the study quality? | Comments |
| Avenell, A., et al. (2009). (56( | yes | na | na | ? | yes | yes |  |
| Jorde, R., et al. (2010). (61) | yes | yes | yes | ? | no | yes | High doses of vitamin D |
| Molgaard, C., et al. (2010). (40 | yes | yes | not reported | ? | ? | No |  |
| Urashima, M., et al. (2010)(66) | no | no | yes | can't tell | na | can't tell |  |

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| **VITAMIN D, SYSTEMATIC REVIEWS** | | |  |  |  |  |  |  |  |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Avenell et al 2009 (35) | A | Vitamin D and vitamin D-related conpound with or without calcium | Hip fracture (primary outcome), non-vertebral, vertebral or any new fracture, adverse effects | RCT and quasi-randomised trials | Elderly (menn over 65 and postmenopausal women). Not restricted to healthy persons | YES (incl. Analouges) | YES | YES | YES |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Bjelakovic et al 2011(57) | A | Vitamin D. Although the review also includes active forms of vitamin D, these results are not included in our SLR | All-cause mortality (primary) | RCT | Yes | YES | YES | YES | YES |
| Black et al 2012 (30) | C | Vitamin D supplements | S-25(OH)D | RCTs | Yes | Yes | Yes | Yes | Yes |
| Cameron et al 2010 (44) | C | Vitamin D and other interventions | rate or number of falls, and fallers | Randomised trials; quasi-randomised trials; trials in which treatment allocation was inadequately concealed. | older people,of either sex, in nursing care facilities or hospitals | Many interventions; vitamin D(with and without calcium) one of these | YES | YES | YES |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Cashman et al 2011 (32) | C | Intervention, vitamin D supplementations | serum or plasma 25(OH)D | Meta analysis based on RCTs | yes | Vitamin D alone or in combinationd with Ca | reported in another publication | yes | yes |

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| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Chung et al 2009(28) | B | Vitamin D (intakes, supplements), 25(OH)D see comments | Growth, CVD, body weight, cancer (total, prostate, colorectal, breast, pancreatic), immunologic outcomes, preeclampsia, other pregnancy related outcomes, rickets, fractures, falls, performance, all-cause mortality, hypertension, blood pressure, bone mineral density, bone mineral content, 25(OH)D | Primary studies (RCT, Nonrandomized prospective comparative studies of interventions, prospective longitudinal observational studies, prospective nested case-control) and systematic reviews | 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, 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. | Vitamin D alone and in combination with calcium | YES | YES | YES, reporting (tables) done by study design in the evidence report | |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** | |
| Cranney et al 2007(27) | B | Vitamin D, 25(OH)D, supplements, fortification | Bone variables, falls, muscle strength, 25(OH)D | Primary studies (RCT, Nonrandomized prospective comarative studies of interventions, prospective longitudinal observational studies, prospective nested case-control) and systematic reviews | YES | Vitamin D alone and in combination with calcium | YES | YES | YES, reporting (tables) done by study design in the evidence report | |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** | |
| De-Regil et al 2012 (33) | A | Supplements with vitamin D alone or in combination with calcium or other vitamins and minerals | maternal and neonatal outcomes | Randomised or quasirandomised studies | Pregnant women; offspring | Supplements with vitamin D alone or in combination with calcium or other vitamins and minerals | Yes | Yes | Yes | |
| Gillespie et al 2009 (45) | A | The review evaluates a variety of interventions. Only vitamin D is reported here. | Primary outcomes: Rate of falls and number of fallers | Randomised controlled trials and quasi-randomised trials | Elderly living in the community | The review evaluates a variety of interventions. Vitamin D (with or without calcium) is reported here. | YES | YES | YES | |

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| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Grandi et al. 2010(62) | A | 25(OH)D | Cardiovascular disease, Incidence and mortality | yes | healthy for incidence, not healthy for mortality | NA | NA | YES | YES |
| IARC 2008 (51) | B/C | Measured 25OHD | Colorectal, breast and prostate cancer and colorectal adenoma | Case-control and cohort studies | YES | - | YES | YES | YES |
| Kalyani et al 2010(43) | C | Vitamin D and vitamin D analouges. | Falls | RCTs | YES, but not only | YES | YES | YES | YES |
| Lerch and Meissner 2007 (34) | A | Any intervention to prevent nutritional rickets. Vit D supplementation/advice to get more sun | Occurence of rickets. Adverse effects. | RCT, quasi-randomized,non-randomized and prospective sohort studies | YES | YES (except one study, Strand) | YES | YES | YES |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Michael et al 2010 (46) | B | Interventions to prevent falling among community-dwelling older adults | Falls/fallers | RCT | Yes | Yes, separate analysis for this purpose | Yes | Yes | Yes |
| Muir et al 2011(49) | B | Vitamin D and vitamin D + calcium | muscle strength, gait and function /balance | RCT | Yes + institutionalised elderly | YES | YES | YES | YES |
| Murad et al 2011(47) | C | Intervention, vitamin D supplementations | Falls | Meta analysis based on RCTs | For some included studies | both | No (Only brief description of total population) | yes | yes |
| Nnoaham and Clarke 2008 (65) | C | Tuberculose | 25(OH)D | Cace-controll, prospective studies | No, TB positive patients | not relevant | YES | YES | YES |
| O´Donnell et al 2008(31) | C | Vitamin D fortification | S-25(OH)D | RCTs | Yes | Yes | Yes | Yes | Yes |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Parker et al. 2010 (54) | C | 25(OH)D | CVD, DM, MetS | Chort, Cross-sectional, case-control | not specified for the prospective studies | not relevant | not relevant | YES | YES |

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| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Pittas et al 2010 (55) | B | Measured 25OHD, self-reported vitamin D intake. Interventions: Vitamin D (with or without calcium), UVB | Cardiometabolic outcomes: Type 2 DM, hypertension, incident CVD | RCT's, cohort and nested-case-control studies | YES | YES | YES | YES |  |
| Stockton et al 2010(48) | B | vitamin D supplementation, all forms and all doses | Muscle strenght | RCTs | For some of the studies YES, not all | Vitamin D alone and in combination with calcium | YES | YES | YES |
| van der Putten et al 2009 (42) | C | 25(OH)D | Peridontal disease | Cross-sectional | not relevant | not relevant | not relevant | YES | YES |
| Wang et al 2010 (63) | C | Vitamin D and calcium | Cardiovascular outcomes | RCTs and prospective studies | general population and patients | YES(one subset on calcium alone) | YES | YES | YES |
| WCRF 2007(50) | C | both | cancers | observational and interventions |  | Vitamin D alone or in combination with Ca | yes | yes | yes |

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| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Vestergaard et al 2009 -*initial search Mosekilde et al 2007 (36)* | C | Vitamin D and vitamin D + calcium | vertebral fractures non vertibral fractures, | RCTs | YES, propably healthy population. | Both vitamin D alone and with calcium | YES | YES | YES |
| Winzenberg *et al.* 2010 (39) | B | vitamin D supplementation | bone mineral density in children | RCTs | YES | Vitamin D | YES | YES | YES |
| Witham et al 2009(59) | C | Vitamin D and vitamin D analouges. UVB radiation | Blood pressure (and cardiac risk factors) | RCT's | Mixture of patients and healthy | YES | YES | YES | YES |
| Wu et al 2010 (60) | C | Vitamin D and analogues, with and without calcium | systolic and diastolic blood pressure | RCTs | normo-and hypertensive | YES( one analogue study) | YES | YES | YES |
| Yamshchikov et al 2009 (64) | C | vitamin D dose (intervention) | Infectious diseases (bacterial, virus, other) | RCTs | patients with infections | vitamin D | YES | YES | YES |
| **Author Year Journal /Source** | **Summary of the study quality** | **Intervention or exposure** | **Outcome** | **Study design included** | **Healthy population at baseline?** | **Concerning intervention studies: Only included Vit D interventions (or in combination with calcium)** | **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)?** |
| Yin et al 2009 (52) | B/C | 25OHD | Colorectal incidence and mortality | Cohort and nested case-control studies | YES | na | YES | Clear endpoint, but the diagnostic prosedures not described | YES |
| Zipitis and Akobeng 2008 (53) | B | Vitamin D supplementation | Diabetes type 1 | Case-countrol, cohort | YES, propably healthy population. | not relevant | no | partly | YES |

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| Table 1. Effect of vitamin D fortification on S-25(OH)D | | | | | | | | | | | | | | |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/ studies | | Age | Sex | | | Vitamin D supplementation or fortification | | total Vitamin D intake | Calcium intake | S-25OHD baseline | S-25OHD final | S-25OHD increment | Methods | Season/ location | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Cranney et al 2007(27) | SLR of RCTs | | Eleven RCTs (N = 1,281) of which seven (N = 668) permitted a quantitative analysis. | adults; | | mixed | Fortified skimmed milk; fortified orange juice ; fortified cheese, fortified bread, nutrient dense fruit and dairy products, high vitamin D diet | | Dietary vitamin D intake was not included; fortification 2,5-25 µg/d | | Some studies included calcium | not recorded | not recorded | 15-40 nmol/L | RIA, HPLC, CBPA, one study no report | Winter: 3; Spring: 1; not reported 7 | 3 weeks- 24 mo | No | Combined data from two trials (N = 275) that were similar in the dietary vehicle used (fortified skim milk), population studied (postmenopausal women and young adults), dose of vitamin D (400 and 480 IU daily), type of vitamin D (D3), 25(OH)D assay (RIA), and outcome (total 25(OH)D) demonstrated a significantly higher absolute change in serum 25(OH)D (WMD 15.71, 95% CI 12.89, 18.53, heterogeneity I2 = 0 percent) in the treatment group. A significantly higher percent change in serum 25(OH)D was demonstrated in the treatment group (WMD 19.13, 95% CI 15.32, 22.95). However, heterogeneity of the treatment effect was high (I2 = 54.1 percent).One demonstrated a decrease in 25(OH)D levels in both groups as a result of seasonal decline. However, food fortification reduced the degree of seasonal decline in the treatment group.. The positive direction of the treatment effect of dietary interventions with foods fortified with vitamin D is consistent. Based on our synthesis of the data from the individual trials, the treatment effect may be dependent on baseline serum 25(OH)D levels. Those trials with low baseline 25(OH)D levels (i.e., < 50 nmol/L)1 consistently demonstrated a greater percent increase in 25(OH)D levelsat the end of study compared to trials with higher baseline 25(OH)D levels (i.e., > 50 nmol/L). | Food fortification with vitamin D resulted in significant increases in serum 25(OH)D concentrations with the treatment effect ranging from 15 to 40 nmol/L. The combined effect of fortified food from two trials with vitamin D3 doses equivalent to 10-12 µg/d was 16 nmol/L (95% CI 12.9, 18.5). |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D supplementation or fortification | total Vitamin D intake | Calcium intake | S-25OHD baseline | S-25OHD final | S-25OHD increment | Methods | Season/ location | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Black et al 2012 (30) | SLR of RCTs | 16 RCTs .(N = 1513, 767 treated and 746 controls | adults; diabetic adults, older adults; range 17-91 | mixed | Orange juice, milk, milk powder skim milk powder,diary products, yoghurt drink, wheat bread | from 3 to 25 mg (per 100 g or serving, or dose achieved from consumption of fortified food): | Some studies included calcium | recorded in all | not recorded in 4 studies | recorded | RIA, HPLC , competitive protein binding assay (CPBA), Roche Elecsys 2010 COBAS system ( , and chemiluminescence immunoassay | Mainly winter months; one april-april, 4 no reported . 7 were conducted at latitudes 40 north. | Four studies were conducted for 1 y or more. 3 wks to 5 months. | Yes in some | A meta-analysis of the absolute mean change in circulating 25(OH)D concentrations was conducted using a random effects model. Sixteen studies from 15 publications were included, of which 14 showed a significant effect of fortified foods on 25(OH)D concentrations. Heterogeneity was high (P =,0.0001, I2 = 89%) and was partly explained by dose, latitude (range, 3–608), and baseline 25(OH)D (range, 24.0–83.6 nmol/L). When combined in a random effects analysis (n = 1513; 767 treated, 746 controls), a mean individual intake of ;11 µg/d from fortified foods (range, 3–25 µg/d) increased 25(OH)D by 19.4 nmol/L (95% CI: 13.9, 24.9), corresponding to a 1.2 nmol/L (95% CI: 0.72, 1.68) increase in 25(OH)D for each 1 µg ingested.When combined with latitude, the treatment effectwas slightly higher in studies conducted $408 compared with those at lower latitude [22.4 (14.8, 30.0) and 17.3 (10.4, 24.3), respectively]. The treatment effect was substantially higher in studies where mean baseline 25(OH)D concentrations were<50 nmol/L compared with those >50 nmol/L [24.9 (15.6, 34.1) and 13.6 (9.5, 17.7), respectively]. The overall treatment effect was 25.9 (19.3, 32.4), which was substantially higher than for those studies using ,10 µg/d [11.6 (6.7, 16.6)]. | Vitamin D food fortification increases circulating 25(OH)D concentrations in community-dwelling adults |

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| **Table 2 Effect of vitamin D supplementation on S-25-OHD** | | | | | | | | |  |  |  |  |  |  |  |
| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D supplementation** | **total Vitamin D intake** | **Calcium intake** | **S-25OHD baseline** | **S-25OHD final** | **S-25OHD increment** | **Methods** | **Season/ location** | **Follow-up time** | **Dietary intake** | **Overall results** |
| Cranney et al 2007 (27) | Systematic review of RCTs | 7 RCTS | Infants | mixed | D2 4 trials; D3 3 trials; In most trials, infants received daily doses ≤ 400 IU of vitamin D2 | ND | ND | not reported in all | yes | not in all | Serum 25(OH)D assays included CPBA in four trials, immunoassay in two and HPLC in one trial. | Season reported in one study | 12 wks to 9 months | No | One trial suggested that 200 IU of vitamin D2 may not be enough to prevent vitamin D deficiency, in some infants residing at northern latitudes. A dose-response was noted in this same 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. |
| Cranney et al 2007 | Systematic review of RCTs | 6 RCTs(40 to 126 women) | Pregnant Women and Lactating Mothers | women | D2 3trials; D2 3 trials ;Dosages ranged from 400 to 1,000 IU. | ND | ND | not reported in all | yes | not in all | Assays for circulating 25(OH)D were CPBA in four trials and RIA in two. | Season reported in some studies | 3 wks to 6 months | No | 1,000-3,600 IU/day of vitamin D2 and 1,000 IU/ d of vitamin D3 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 1,000 IU of vitamin D2 during winter months did not increase serum 25(OH)D concentrations in the infants. |
| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D supplementation** | **total Vitamin D intake** | **Calcium intake** | **S-25OHD baseline** | **S-25OHD final** | **S-25OHD increment** | **Methods** | **Season/ location** | **Follow-up time** | **Dietary intake** | **Overall results** |
| Cranney et al 2007(27) | Systematic review of RCTs | 4 RCTs | Children and adolescents; xx prepubertal; xx pubertal | mixed | Vitamin D2 in one trial, D3 in 3.Doses ranged from 200 to 2,000 IU per day. | ND | ND | yes | yes | yes | CPBA in three; RIA in one | Season eported in some studies | 4 wks to one year | No | There were consistent increases in 25(OH)D concentrations ranging from 8 nmol/L (200 IU), 16.5 (with 600 IU D3) to 60 nmol/L (2,000 IU of vitamin D3). |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D supplementation | total Vitamin D intake | Calcium intake | S-25OHD baseline | S-25OHD final | S-25OHD increment | Methods | Season/ location | Follow-up time | Dietary intake | Overall results |
| Cranney et al 2007(27) | Systematic review of RCTs | 9RCTs | premenopausal women and young men | mixed | Vitamin D3 in 8 RCTs, 3 compared the effect of vitamin D3 to D2. Doses ranged from 6000 IU per day to 10 000 IU per day(vitamin D3). Vitamin D2: 4000 IU daily to 10 0 000 IU ( single dose) | ND | as supplement in two studies | all except one | yes | yes in those wiht baseline | CPBA in three; RIA or HPLC in the others | Season eported in some studies | 4 wks to 5 months | No | Three trials found that vitamin D2 and D3 in healthy adults may have different effects on serum 25(OH)D concentrations. Vitamin D2 appeared to have a smaller effect on serum 25(OH)D, which may have been due to more rapid clearance and/or different metabolism than vitamin D3. One trial compared 100,000 IU vitamin D2 orally versus injection and found a greater variability in response with the intramuscular preparation. A dose-response effect was noted in those trials that used multiple doses of vitamin D3. |
|  |  | Meta-analyses was conducted in 17 RCTs giving oral vitamin D supplementation with or without calcium vs placebo or calcium on the absolute change in 25(OH)D and absolute change by dose. They concluded that: The treatment effect of oral vitamin D3 supplementation increases with increasing doses. Combining trials by different clinical and methodological characteristics did not change the direction of this effect nor did it reduce the heterogeneity found. Meta-regression results demonstrated significant association between dose and serum 25(OH)D levels (p = 0.04). The meta-regression (exploratory only) results suggested that 100 IU of vitamin D3 will increase the serum 25(OH)D concentrations by 1-2 nmol/L. This suggests that doses of 400-800 IU daily may be inadequate to prevent vitamin D deficiency in at-risk individuals. Vitamin D3 doses of 700 IU daily or more significantly and consistently decreased serum concentrations of PTH in vitamin D deficient populations. | | | | | | | | | | | | | |

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| **Reference** | **Study type** | **Number of subjects/ studies** | **Age** | **Sex** | **Vitamin D supplemen**  **tation** | **total Vitamin D intake** | **Calcium intake** | **S-25OHD baseline** | **S-25OHD final** | **S-25OHD increment** | **Methods** | **Season/ location** | **Follow-up time** | **Dietary intake** | **Overall results** |
| Cashman et al 2011(32) | Systematic review of RCTs | 44 RCTs; meta-regression included only those performed at latitudes > 49,5 ⁰ N | 8-85 yrs | mixed | D2 and D3/ less than 50 µg/d; oral dosing; calcium included in some studies | Reported in the meta-regression studies; some estimated from earlier studies in the same country and age group | ND | Meta-regression studies :mean 24.6- 76.9 nmol/l | Meta-regression studiess : in supplemented groups 55-90.1 nmol/l | Estimated | CPBA, EIA, RiA,HPLC | winter | 8-52 weeks | Included | A combined weighted linear model meta-regression analyses of natural log (Ln) total vitamin D intake (i.e. diet and plemental vitamin D) v. achieved serum 25(OH)D in winter) produced a urvilinear relationship (mean (95% lower CI) serum 25(OH)D (nmol/l) ¼=9.2 (8.·5) Ln (total vitamin D)). Use of non-transformed total vitamin D intake data (maximum 1400 IU/d; 35mg/d) provided for a more linear relationship (mean serum 25(OH)D (nmol/l) ¼ 0·044 £ (total vitamin D) þ 33·035). Although inputting an intake of 600 IU/d (i.e. the RDA) into the 95% lower CI curvilinear and linear models predicted a serum 25(OH)D of 54·4 and 55·2 nmol/l, respectively, the total vitamin D intake that would achieve 50 (and 40) nmol/l serum 25(OH)D was 359 (111) and 480 (260) IU/d, pectively. Inclusion of 95% range in the model to account for inter-individual variability increased the predicted intake of vitamin D needed to maintain serum 25(OH)D $50 nmol/l to 930 IU/d. |

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| Summary table 3. Pregnancy end points | | | | | | | | | | | |
| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung, M., et al. 2009 (28) | SLR | One nested case control study on maternal vitamin D status and preeclampsia | pregnant women | Female | Not reported | Not reported | Less than 37.5 nmol/L at baseline compared with higher levels | Gestation period from early pregnancy | not reported | Mothers with baseline levels less than 37.5 nmol/L higher risk of preeclampsia | No conclusions drawn |
| De-Regil LM et al 2012 (33) | SLR of RCTs | 1023 subjects/6 trials | Pregnant women | Female | Supplements of 20 to 30 µg on a daily basis. Also one arm of two trials included a single 5000µg dose in third trimester, and one trial 15000µg twice, during 7th and 8th month of pregnancy | not reported | s-25OHD was measured in four trials, showing that women who receive vitamin D had higher s-25-OHD at term compared with placebo or no intervention. | Pregnancy through the neonatal period | not reported | Mean difference in 25OHD at term between supplemented and placebo groups was 49.70nmol/L; 95%CI 21.86 to 77.54. Risk for low birthweight (less than 2500g) in treatment vs. placebo suggest a trend favoring supplementation, with borderline statistical significance, average risk ratio 0.48; 95%CI 0.23 to 1.01. No studies reported on pre eclampsia or gestational diabetes. For maternal secondary outcomes, one study reported on nephritic syndrome, suggesting that women receiving supplements were not as likely to report nephritic syndrome as a side effect as women receiving placebo (RR 0.17; 95% CI 0.01 to 4.06). For infant secondary outcomes, two trials reported on birth length, showing no difference between groups. For head circumference, two trials suggest a small effect of vitamin D supplementation (MD 0.43 cm; CI 0.06 to 0.79cm). One study reported on stillbirth as well as neonatal deaths showing no difference between the groups, but scarcity of data prevent firm conclusions. | There is currently insufficient high quality evidence relating to the clinical effects of vitamin D supplementation during pregnancy. |

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| **Summary table 4. Growth end point** | | | | | | | | | | | |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Chung, et al. 2009(28) | SLR | eight interventions and 2 observational studies | Newborns, infants and children, up to age 17 | Both sexes |  |  |  |  |  |  |  |
|  |  |  |  |  | **Trials**: Dietary intake reported in one trial in India. Supplements differed from 100IU/d to 1200IU/d and to 600,000/month during 7th and 8th month of pregnancy | Not reported | not reported | until delivery for pregnant, 7 mo for lactating and 1 year for adolescent girls | not reported | No significant differences found between intervention and controls in six of the trials. Two trials in India found siginficant increases in birth weights and lengths of infants where pregnant women received 1.2 million units total in last trimester. Net difference in birth weight in trial 1: +190 g CI 90, 290; trial 2: +410 g, CI 166,654. |  |
|  |  |  |  |  | **Cohort studies**: | not reported | yes | study 1: until delivery , study 2: to age 9 years | not reported | No significant associations with growth outcomes, birth weights, lengths or height at 9 months or 9 years related to 25(OH)D in either study, study 1: N=374, study 2: N=466 (178 at 9 year follow up) |  |

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| **Summary table 5. Rickets** | |  |  |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Lerch & Meissner 2012 (34) | Cochrane review of RTC's (3 RCT's (incl. 2 cluster randomized) and one non-randomized trial).Aim: 'To assess the effects of various interventions on the prevention of nutritional rickets in term born children' | Four trials, n=676, 757, 66, 259 | One month to 15 yrs. | Both | Vit D vrs. no intervention; milk vrs. milk + vit D vrs. no intervention; vit D vrs. placebo; combined intervention (vit D, calcium, counseling) |  |  | 6 months to 2 yrs |  | In one of the studies (Turkey, children up to three years of age), none in the intervention group (400 IU vit D per day for 1 year) developed rickets compared to 14 of 374 children in the control group. In the study with combined intervention (China,children up to three years of age) (incl. 300 IU vit D), the RR of rickets was 0.76 (95% CI 0.61-0.95). In two of the studies, no cases of rickets occurred | Authors’ conclusions: 'There a only few studies on the prevention of nutritional rickets in term born children. Until new data become available, it appears sound to offer preventive measures (vitamin D or calcium) to groups of high risk' Comment:Limited to studies performed the last 50 years. The included studies had methodological weaknesses |

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| **Reference** | **Study type** | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung et al. 2007(27) | SLR, Referring to results from Cranney et al(2007) which Chung build on. Aim: '‘Are there specific concentrations of serum 25(OH)D that are associated with established vitamin D deficiency rickets in infants and young children? | One RCT, 4 before-after studies and 8 cases-control studies. Ranging from 9-123 participants. | ≤ 5 years (if older children the majority was below 5 yrs.) | both |  |  |  |  |  | In 6 studies, mean or median 25(OH)D in children with rickets was < 30 nmol/l, whereas it was between 30-50 nmol/l in the other studies. | Chung et al's conclusion: ‘The Ottawa EPC report concluded that there is “fair” evidence, regardless of the type of assay, for an association between low serum 25(OH)D concentrations and confirmed rickets. According to the report, there is inconsistent evidence regarding the threshold concentration of serum 25(OH)D above which rickets does not occur. Our updated search did not identify new studies examining the association between vitamin D and rickets’ Comment:Most studies were conducted in developing countries with low dietary calcium intake. Low calcium intake can influence on the relation between 25(OH)D and rickets, and the 25(OH)D threshold for rickets in populations with high calcium intake (like in North America) is unclear |

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| **Table 6. Summary table, vitamin D alone and vitamin D in combination with calcium and fractures** | | | | | | | | | | | | | | | |
| **Reference** | **Study type** |  |  | | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Vestergaard et a l2010 (36) | This is predominantly a review of reviews with no additional meta-analysis | |  | |  |  | Predominantly postmenopausal women |  |  |  |  |  |  |  |  |
|  |  | | Vitamin D alone versus placebo or no treatment | The results from our reference 143 (Avenell et al (2009)) is reported. In addition, the results form the DIPART study (ref) is described. As in Avenell et al., no significant effect of vitamin D alone compared to placebo/no vitamin D was found for any fracture or hip fracture (doses of vitamin D 400-800 IU).The review also reports the results from a RCT published in 2010 (ref, Sanders et al.) in 2258 women, aged 70 years or older. A single high-dose of vitamin D3 (12,500 micrograms [500,000 IU]) or placebo was given orally once a year over 3 to 5 years. Vitamin D3 significantly increased the risk for any fracture compared with placebo (RR 1.26, 95% CI 1.00-1.59; p = 0.047). In addition, the incidence of falls was significantly increased in the vitamin D3 group compared to placebo (RR 1.15, 95% CI 1.02 -1.30). The increased incidence of falls was most prominent the first 3 months after dosing with vitamin D3 (first 3 months: RR 1.31; last 9 months: RR 1.13). | | | | | | | | | | Authors conclusion: 'Unlikely to be benificial' |  |
|  |  | | Vitamin D plus calcium versus placebo or no treatment | The results from our reference 143 (Avenell et al (2009)) is reported. In addition, the results form the DIPART study (ref) is described. In this patient level pooled analysis of seven major vitamin D fracture trials with 68500 participants, the overall risk of fracture was reduced in those given combined supplementation with vitamin D (400-800 IU) and calcium compared to placebo/no vitamin D (HR 0.92, 95% CI 0.86-0.99). The risk of hip fracture was HR 0.84, 95% CI 0.70-1.01 (later corrected to HR 0.83, 95% CI 0.69-0.99 due to a coding error in the original publication, conf. BMJ 2010;340:b5463). In subgroup analyses, the significant effect was found in studies giving 10 but not 20 ug vitamin D. Reviews by Bischoff-Ferrari et al from 2005 (ref) and 2009 (ref) were also referred to. In the first they reported that vitamin D (17.5-20 ug vit D/day or 100 000 IU every 4 months) plus supplemental calcium reduced the risk of non-vertebral fractures and hip fracture. In the other one (from 2009), studies with vitamin D alone and vitamin D plus calcium was combined, and there was no separate analysis of vitamin D plus calcium versus placebo. It suggested that increasing doses of vitamin D may be related to reduced fracture risk. | | | | | | | | | | Authors conclusion: 'Likely to be benificial' |  |

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| **Reference** | **Study type** |  |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Avenell et al 2009 (35) | SLR |  |  |  | Men over 65 years of age and post-menopausal women. | |  |  |  |  |  |  |  |  |
|  |  | Vitamin D alone versus placebo or no treatment |  | A total of ten trials |  |  | Up to 1100 IU daily vrs. placebo or no treatment |  |  | 1 - 5,2 yrs |  |  | Vitamin D alone in the doses tested out appears unlikely to be effective in preventing hip fracture, vertebral fracture or any new fracture |  |
|  |  |  | Hip fracture | Nine trials, 24,749 participants, |  |  |  |  |  |  |  | RR 1.15, 95%CI 0.99-1.33 |  |  |
|  |  |  | Vertebral fx or deformity | Five trials, 9138 participants |  |  |  |  |  |  |  | RR, random effects, 0.90, 95% CI 0.42 to 1.92 |  |  |
|  |  |  | Any new fracture | Ten trials, 25,016 participants |  |  |  |  |  |  |  | RR 1.01, 95% CI 0.93 -1.09 |  |  |
|  |  | Vitamin D with calcium versus calcium alone | na? |  |  |  |  |  |  |  |  |  |  |  |
|  |  | Vitamin D versus calcium | na? |  |  |  |  |  |  |  |  |  |  |  |

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| **Reference** | **Study type** |  |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Avenell et al (2009), cont. (35) |  | Vitamin D plus calcium versus placebo or no treatment |  |  |  |  | 400 to 800 IU vitamin D3 with co-administration of calcium (500-1600 mg/d?) |  |  |  |  |  | Vitamin D with calcium reduced the risk of hip fracture, whereas the effect on non-vertebral fracture was borderlinge significant (p=0.052). | Subgroup analysis showed a significant reduction in hip fractures in institutionalized but not in community-dwellers, but the interaction was not significant |
|  |  |  | Hip fracture | Eight trials, 46,658 participants |  |  |  |  |  |  |  | RR 0.84, 95% CI 0.73-0.96 |  | Subgroup analysis: Significant effect in institutionalized elderly (RR 0.75, 95% CI 0.62 - 0.92), but not in the community dwellers ( RR 0.91, 95% CI 0.76 - 1.08). However, not sign.interaction, p=0.15 |
|  |  |  | Vertebral fx | Three trials, 38,990 participants |  |  |  |  |  |  |  | RR 0.91, 95% CI 0.75-1.11 |  |  |
|  |  |  | Non-vertebral fracture | Nine trials, 46,781 participants |  |  |  |  |  |  |  | **RR 0.95, 95% CI 090-1.00** |  | Subgoup analysis: Significant effect in institutionalized elderly (RR 0.85, 95% CI 0.74 to 0.98), but not in the community dwellers ( RR 0.97 95% CI 0.91 to 1.02). The interaction was not significant (p=0.09) |

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| **Reference** | **Study type** |  |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Chung et al 2009 (28) | SLR, Refering to results from Cranney et al(2007) SLR which Chung build on | Oral vitamin D2or3 +/- calcium versus calcium or placebo |  |  | Postmenopausal women and elderly men | |  |  |  |  |  |  |  | Subgroup analysis by dosage of vitamin D (trials ≥ 800 IU versus those trials using < 800 IU/day) did not explain treatment effect. Citation:Combining the results from four trials of vitamin D3 180,181,184,231 that had end of study 25(OH)D concentrations of >74 nmol/L was consistent with a significant reduction in total fractures [OR 0.73 (95 % CI 0.63-0.85), I2 = 0] compared to a non-significant reduction when combining results of trials with end of study 25(OH)D concentrations of < 74 nmol/L'....'This needs to be interpreted with caution given the variability in the 25(OH)D assays and incomplete assessment of vitamin D status in the fracture trials'.Added in Chung et al: Findings from one additional C-rated RCT reported no significant effects of vitamin D with calcium versus calcium alone on fracture (ref) |

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| **Reference** | **Study type** |  |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Chung et al 2009 ,cont. (28) |  |  | Hip fracture | not presented |  |  |  |  |  |  |  |  |  |  |
|  |  |  | Vertebral fractures | Three trials, 44260 participants |  |  |  |  |  |  |  | OR 0.88, 95%CI 0.73-1.07 |  |  |
|  |  |  | Total fractures | 13 trials, 58,712 participants |  |  |  |  |  |  |  | OR 0.90, 95% CI 0.81-1.02 |  | Subgoup analysis: Significant effect in institutionalized elderly (OR 0.73, 95% CI 0.61 - 0.88), but not in the community dwellers ( OR 0.95, 95% CI 0.86 - 1.05). |
|  |  | Vitamin D3 alone versus placebo |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | Hip fracture | Three trials, 7939 participants |  |  |  |  |  |  |  | OR 1.11, 95% CI 0.86-1.44 |  |  |
|  |  |  | Vertebral fx or deformity | not presented |  |  |  |  |  |  |  |  |  |  |
|  |  |  | Non-vertebral fractures | Three trials, 7939 participants |  |  |  |  |  |  |  | OR 0.99, 95%CI 0.83-1-17 |  |  |
|  |  |  | Total fractures | Three trials, 7939 participants |  |  |  |  |  |  |  | OR 0.98, 95%CI 0.79-1.23 |  |  |

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| **Reference** | **Study type** |  |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** | **Comments** |
| Chung et al 2009, cont.(28) |  | Vitamin D3 plus calcium versus placebo or no treatment |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  | Hip fracture | Seven trials, n=46,07 |  |  |  |  |  |  |  | OR 0.83, 95%CI 0-68-1.00, p=0.05 |  | Subgoup analysis: Significant effect in institutionalized elderly (OR 0.69, 95% CI 0.53 - 0.90). |
|  |  |  | Vertebral fx or deformity | not presented |  |  |  |  |  |  |  |  |  |  |
|  |  |  | Non-vertebral fractures | Seven trials, n=46,07 |  |  |  |  |  |  |  | OR 0.87, 95% CI 0.75-1.00, p=0.05 |  |  |
|  |  |  | Total fractures | Seven trials, n=46,07 |  |  |  |  |  |  |  | OR 0.87, 95% CI 0.76-1.00, p=0.05 |  |  |
|  |  |  | 25(OH)D |  |  |  |  |  |  |  |  | Based on observational studies , the evidence for an association between serum 25(OH)D and the risk of fractures is inconsistent. |  |  |

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| **Summary table 7. Vitamin D and bone mineral content/ bone mineral density** | |  |  |  |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung et al 2007 (27) | SLR, Referring to results from Ottawa SLR(Cranney et al 2007) which Chung build on |  |  |  |  |  |  |  |  |  |  |  |
|  | SLR of RCT's and observational studies. | Serum 25OHD and bone health outcomes in infants (Q 1A, part 2).No new data since theCranney et al(2007) report. | 3 RCT (n ranging from 18-80 infants), 4 case-control studies (n ranging from 21-82 infants). | Infants | both | RCT's: 400 IU vrs. placebo (2 studies), 1000IU vrs. 500 IU (1 study). All studies used vitamin D2 |  |  | RCT's: 3-6 mnd |  | One of the RCT's found no benefit on radial BMC. The other found a transient increase in the intervention group at 12 weeks but not at 26 week. Based on 3 case-control studies (and of the 2 RCT above) a threshold value for rise in PTH may exist around 27 nmol/l. Higher 25OHD was related to greater whole body BMC and lower lumbar BMC. | The evidence for an association between specific concentrations of 25OHD and BMC in infants is inconsistent. Fair evidence for an inverse relation between 25OHD and PTH at low levels of 25OHD. A threshold may exist around 27 nmol/l |

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| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
|  |  | Serum 25OHD and bone health outcomes in older children and adolescents (Q 1A, part 3) | 3 studies in older children (1 RCT, 1 cohort and 1 before and after study). 4 studies in adolescents (1 RCT, 2 Cohort and 1 cases-control study). One of the studies did not assess BMC/BMD but only PTH | Older children (6-10 yrs) and adolescents (9-16 yrs) | both | RCT's 400 IU/day, 14000/week, 14000 IU/week | RCT's: No co-intervention with calcium |  | 12-13 months |  | No studies assessed the relation between s-25OHD and fracture. In a RCT 400 IU vit D did not impact distal radius BMC in pre-pubertal Finnish girls after 13 months. 3 studies in older children or adolescents reported an inverse relation between 25OHD and PTH plateauing at 75-83 nmol/l in two studies and 30 nmol/l in one study. 2 of 3 studies reported a positive relation between baseline 25OHD and BMC/BMD. One RCT (1400IU/week, 14000 IU/week, placebo) with Jadad score 4/5 showed a relation between baseline 25(OH)D and BMD, but only high dose of vitamin D supplementation increased total hip BMD. In a cohort study, maternal vitamin D status was weakly related to whole body and spine BMC in 9 yrs old children | Author's conclusion: 'There is fair evidence for an inverse relationship between serum 25(OH)D concentrations and serum PTH in older children and adolescents, with a plateau of PTH at serum 25(OH)D levels ranging from above 30 to 83 nmol/L. There is fair evidence that circulating 25(OH)D levels are associated with change in BMD/BMC from studies in older children and adolescents. Results from two RCTs did not confirm a consistent benefit of vitamin D supplementation across all BMD sites.' 'The measures used to assess bone mineral (BMC/BMD) in older children and adolescents have not been directly shown to predict bone health outcomes in adulthood' The Ottava report also refers to a Finnish study published after their search (Viljakainen et al 2006) in 228 adolescent girls intervened with two doses of vitamin D3 (200 and 400 IU daily) compared to placebo. A positive effects on BMC at mean serum 25(OH)D > 50 nmol/l was reported. Comment: Two new RCTs in healthy girls did not find any effect of 200 IU vit D + 1 g calcium over 2 years (168 girls, Beirut) or 400 IU , 800 IU or placebo over one year (26 Pakistani girls in Copenhagen). Quality: C |

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| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
|  |  | Serum 25OHD and bone health outcomes in postmenopausal women and older men (Q 1C) | 19 studies (6 RCT's, 7 cohort and 6 case-control) | postmenopausal women and older men | both |  |  |  |  |  | In five RCTs and three cohort studies no association between s-25(OH)D and BMD or bone loss was found. A significant association between 25(OH)D and bone loss was found in four cohort studies, most evident at the hip sites. The evidence for a relation between s-25(OH)D and BMD in the lumbar spine was weak. An association between 25(OH)D and BMD was suggested in six case-control studies, and the association was most consistent for femoral neck BMD. | Authors conclusion: 'There was discordance between the results from RCTs and the majority of observational studies that may be due to the inability of observational studies to control for all relevant confounders. 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. Specific circulating concentrations of 25(OH)D below which bone loss at the hip was increased, ranged from 30-80 nmol/L' |

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| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
|  | SLR of RCTs | Effect of vitamin D supplementation on bone density in women of reproductive age and postmenopausal women and Elderly Men (Q 3A) | 17 trials, 58,712 participants | postmenopausal women and older men | both (but predominately women) | Most trials ≤ 800IU/day | Most trials used calcium (≥ 500 mg) as co-intervention. Only 3 studies used vit D alone |  | Most trials 2-3 years |  | Cranney: Vit D3 + calcium showed a small effect on lumbar spine, femoral neck and total body BMD. There was no effect of vitamin D alone versus placebo, except for one trial. There was no difference between vitamin D + calcium compared to calcium alone | Good evidence that vit D + calcium supplementation leads to a small increase in spine, femoral neck, total hip and total body BMD. Based on these studies it is less certain that vit D alone has an effect on BMD . Comment: One new RCT in postmenopausal women (n=256 elderly women, 1000 IU D2/day + 1,2 g calcium vrs. calcium over one year) and one in Pakistanin men and women in Copenhagen (n 172; 400 IU , 800 IU or placebo over one year). Result: No sign. effect on BMD |
| Winzenberg et al 2011(39) | Cochrane review of RTC's with treatment lasting for at least 3 months | Aim 'To determine the effectiveness of vitamin D supplementation for improving bone mineral density in children' | 6 trials, 541 persons receiving vitamin D and 343 placebo; Two of the studies in white populations, two in Hong Kong, two in Lebanon and one in Pakistanis in Denmark | 8 to 17 yrs | both | Vitamin D3, with the dose administered ranging from 133 IU daily to 14000 IU per week | Two of the studies gave calcium to all groups, else none | Mean levels 17-49 nmol/l at baseline | 1-2 years |  | Overall no significant effect of vitamin D supplementation on total body BMC, hip BMD or forearm BMD, whereas a small effect on lumbar BMD was suggested. In studies with participants with low se-25OHD (≤ 35 nmol/l), a significant effect of supplementation was found for total body BMC and lumbar BMD | Authors’ conclusions: 'These results do not support vitamin D supplementation to improve bone density in healthy children with normal vitamin D levels, but suggest that supplementation of deficient children may be clinically useful. Further RCTs in deficient children are needed to confirm this.' |

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| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Mølgaard et al 2010(40) | RCT (double-blind) |  | 221 | 10-11 yrs | girls | Intervention with 5ug/d or 10ug/d vitamin D over one year versus placebo. Recruited and included throughout the year. | Mean intake around 1000 mg/d | Baseline mean level around 43 nmol/l | 1 year |  | Althoug 25(OH)D increased in the two intervention groups versus placebo, there was no overall effect on BMC and BMD (whole body and lumbar spine) of the intervention. An effect on BMD was repported in the FF VDR genotype subgroup, but the implication of this finding is unclear | No effect of the intervention on BMC or BMD |

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| **Summary table 8. Vitamin D and dental health** | | | |  |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| van der Putten et al 2009(42) | SLR | SR on several nutrients and periodontal disease, only one of the included original papers was on vitamin D |  |  |  |  |  |  |  |  | Inverse association in cross-sectional data from the NHANES III study : Those in the lowest quartile of 25(OH)D had 0.39 mm (men) and 0.26 mm (women) higher clinical attachment loss compared to those in the highest quintile | The authors conclude that the relation between vitamin D and periodontal disease in elderly is unknown and not well researched |

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| Summary table 9. Vitamin D and falls | | |  |  |  |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake/supplementation | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Cameron et al 2010(44) | SLR of RCTs | 5 RCTs/5095 participants. Total 41 RCTS; different interventions.Older people in nursing care facilities and hospitals. Outcome falls or fallers | > 65 yrs | mixed | Vitamin D3 or vitamin D2 (200-800 IU; | Included in some( check), | Not reported in all | 5 months to 2 yrs | No | A positive effect of vitamin D supplementation in reducing rate of falls (Analysis 5.1: RaR 0.72, 0.95% CI 0.55 to 0.95, vitamin D +/- calcium vs no vitamin D supplements), but not for reducing risk of falling(numbers of fallers) (Analysis 5.2: RR 0.98 95% CI 0.89 to 1.09,vitamin D +/- calcium vs no vitamin D supplements) was found. 25(0H)D was low for all patients included in these studies. | Vitamin D supplementation is effective in reducing the rate of falls in nursing care facilities |
| Chung et al 2009 (28) | SLR of 3 cohorts and 1 RCT( Cranney et al) , one case-control + 2 additional RCTs | SLR of 3 cohorts and 1 RCT( Cranney et al) , one case-control + 2 additional RCTs | Elderly | mixed |  |  |  |  |  | 51 – 70 y The Cranneyet al(2007) 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 this report. age ≥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 Cranney et al(2007) 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 Cranney report | The Cranney et al 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 Cranney et al(2007) 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 Cranney et al (2007)report |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake/supplementation | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Gillespie 2009 (45) | SLR of RCTs | 13 RCTs | Older people(> 60 yrs) community dwellers | mixed | vitamin D? | Included in some | In 10 trials | ? | No | The overall analysis of vitamin D versus control did not show a statistically significant difference in rate of falls (RaR (random effects) 0.95, 95% CI 0.80 to 1.14; 3929 participants, 5 studies, risk of falling (RR (fixed effect) 0.96, 95% CI 0.92 to 1.01; 21,110 participants, 10 studies,), or risk of fracture (RR 0.98, 95% CI 0.89 to 1.07; 21,377 participants, 7 studies. s. Post hoc subgroup analysis was done. The rate of falls was significantly reduced in trials recruiting participants with lower vitamin D levels (RaR 0.57, 0.37 to 0.89; 260 participants, 2 trials) but not in participants not so selected (RaR 1.02, 95% CI 0.88 to 1.19; 3669 participants, 3 trials). There was a significant difference between these two subgroups with a greater reduction in rate of falls in the subgroup of trials only recruiting participants with lower vitamin Dlevels (P= 0.01). There was insignificant heterogeneity in the analysis for risk of falling (Analysis 6.2), which was significantly reduced in the lower vitamin D group (RR 0.65, 95% CI 0.46 to 0.91; 562 participants, 3 trials) but not in those not so selected (RR 0.97, 0.92 to 1.02; 20,548 participants, 7 trials). The test for subgroup differences was significant (P = 0.02). | Overall, vitamin D did not reduce falls but may do so in people with lower vitamin D levels. Comment: Vitamin D with or without calcium not separated in analyses |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake/supplementation | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Kalyani et al 2010 (43) | SLR of 10 RCTs | 10 RCTs ; | Mean age 72- 92 | One study included males | 3 ergocalcierol; 6 cholecalciferol; 1 alfacalcidiol ; 7 > 800 IU; 3< 800 IU | 7 studies | Baseline reported in all studies; 2 studies reported change | < 6 months 4 studies ; >6 months 6 studies | No | In pooled analysis, vitamin D therapy (200-1,000 IU) resulted in 14% (relative risk (RR)=0.86, 95% confidence interval (CI)=0.79-0.93; I(2)=7%) fewer falls than calcium or placebo (number needed to treat =15). The following subgroups had significantly fewer falls: community-dwelling (aged <80), adjunctive calcium supplementation, no history of fractures or falls, duration longer than 6 months, cholecalciferol, and dose of 800 IU or greater. Meta-regression demonstrated no linear association between vitamin D dose or duration and treatment effect. Post hoc analysis including seven additional studies (17 total) without explicit fall definitions yielded smaller benefit (RR=0.92, 95% CI=0.87-0.98) and more heterogeneity (I(2)=36%) but found significant intergroup differences favoring adjunctive calcium over none (P=.001). | Vitamin D treatment effectively reduces risk of falls in older adults. |
| Michael et al 2010 (46) | SLR of a previous review (2003) and RCTs | 9 trials/ 5809 participants | Unspecifed in five/ high risk) 4 unselected but > 65 yrs | 5 trials women; 4 mixed | 10-1000IU; One study 600 000 IU(im). D2 or D3? | 6 trials included Ca suppl | ? | 8 weeks to 3 years; median 12 months | No | Vitamin D with or without calcium was associated with a 17% (CI, 11% to 23%) reduced risk for falling during 6 to 36 months of follow-up .Trials of vitamin D with calcium compared with no treatmentor placebo did not support any added benefit of calcium. Comment: Control groups: placebo group, nothing, or calcium.. Age, sex , history fo falling or risk status did not affect the pooled estimate. | Vitamin D treatment without or with calcium reduces risk for falling. |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake/supplementation | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Murad et al 2011 (47) | SLR of 26 RCTS | 26 RCTS 45782 participants | mean age 76 yrs | mixed(78 % women | vitamin D2 8 studies; vitamin D3 18 studies | 10 studies | included in 15; post 11 | 1-62 months | No | Vitamin D use was associated with statistically significant reduction in the risk of falls (odds ratio for suffering at least one fall, 0.86; 95% confidence interval, 0.77–0.96). This effect was more prominent in patients who were vitamin D deficient at baselineandin studies in which calciumwascoadministered with vitamin D.Thequality of evidence was low to moderate because of heterogeneity and publication bias. | Vitamin D combined with calcium reduces the risk of falls. The reduction in studies without calcium coadministration did not reach statistical significance. The majority of the evidence is derived from trials enrolling elderly women. |

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| Summary table 10. Vitamin D and muscle strength | | | | |  |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Stockton et al 2010 (48) | SLR of 17 RCTs | 5072 subjects/ 17 studies | over 50; mainly over 70 | mixed | Vitamin D2 and D3; between 10 µg/day to 15 000 µg as a single dose; one study with calcitriol; one sunlight | In 8 studies; | 13 had control and treatment end of trial | 12 weeks to five years | No | Meta-analysis showed no significant effect of vitamin D supplementation on grip strength (SMD −0.02, 95%CI −0.15,0.11) or proximal lower limb strength (SMD 0.1, 95%CI −0.01,0.22) in adults with 25(OH)D levels >25 nmol/L. Pooled data from two studies in vitamin D deficient participants (25(OH)D <25 nmol/L) monstrated a large effect of vitamin D supplementation on hip muscle strength (SMD 3.52, 95%CI 2.18, 4.85). Comment: Different outcome variables. Calcium was not separated | Vitamin D supplementation does not have a significant effect on muscle strength in adults with baseline 25OHD > 25 nmol/l. However, a limited number of studies demonstrate an increase in proximal muscle strength in adults with vitamin D deficiency. |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Muir et al 2011 (49) | SLR of 13RCTs | c. 2400 subjects,/13 studies | older than 60 yrs; mean 78(sd 4.1),range 63-90 | mixed, mostly women | Vitamin D2 or D3; +/- calcium; doses <20 µg; >20 µg; daily, single or monthly dose; one calcitriol | In 8 studies; | Baseline in 12; followup in 10 | 2 months- 36 months | No | In the pooled analysis, vitamin D supplementation yielded a standardized mean difference of 0.20 (95% confidence interval (CI) = 0.39 to 0.01, P = .04, I2 = 0%) for reduced postural sway, 0.19 (95% CI = 0.35 to 0.02, P = .03, I2 = 0%) for decreased time to complete the Timed Up and Go Test, and 0.05 (95% CI = 0.11 to 0.20, P = .04, I2 = 0%) for lower extremity strength gain. Regarding dosing frequency regimen, only one study demonstrated a beneficial effect on balance with a single large dose. All studies with daily doses of 20 µg or more demonstrated beneficial effects on balance and muscle strength. Comment: Different outcome variables. Calcium was not separated. | Supplemental vitamin D with daily doses of 20 to 25µ consistently demonstrated beneficial effects on strength and balance. An effect on gait was not demonstrated, although further evaluation is recommended. |

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| Summary table 11. Total cancer | | | | | | | | | | | |
| *Reference* | *Study type* | *Number of subjects/*  *studies* | *Age* | *Sex* | *Vitamin D intake* | *Cacium intake* | *S-25OHD* | *Follow-up time* | *Dietary intake estimation* | *RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.* | *Overall results* |
| Chung et al 2009 (28) | SLR of RCTs and Cohorts | two RCTs and two cohorts | adults | both | 1000 IU per day, 100.000 IU/4 mo | Ca citrate 1400 mg or carbonate 1500 mg | <50 up to >120 nmol/l | 4-5 years | na | Both RCTs were conducted on older adults (postmenopausal women in one of the RCTs and people > 70 years in the other) They found no significant effects for vitamin D supplementation (1000 IU/d + Ca vs. only Ca-supplements or 100.000 IU every 4 months vs. placebo). No significant association between baseline serum 25(OH)D concentrations and total cancer mortality. | No significant effect was found. |
| *Reference* | *Study type* | *Number of subjects/*  *studies* | *Age* | *Sex* | *Vitamin D intake* | *Cacium intake* | *S-25OHD* | *Follow-up time* | *Dietary intake estimation* | *RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.* | *Overall results* |
| IAR*C* 2008 (51) | Cohorts | three cohort studies | 17 years or older | both | na | na | Not given in the SR for one of the cohorts. Effect of levels > 37.5 nmol/l or the increment of 25nmol/l | 6-14 years | na | One cohort showed no effect on serum 25(OH)D on total cancer and one study found a significant two fold increased risk for cancer deaths in subjects (patients referred to coronary angiography) with 25(OH) D levels below 37.5 nmol/l. The third cohort found that an increment of 25nmol/l was significantly associated with 17 % reduction in cancer incidence and 29% reduction in cancer mortality. | No overall conclusion is given in the SR regarding total cancer |

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| Summary table 12 Colon/ Colorectal cancer | | | | | | | | | | | |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Cacium intake | S-25OHD | Follow-up time | Dietary intake estimation | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Yin et al 2009 (52) | SLR - report | seven nested case-control study and one cohort study | 17-79 years | both | na | na | 4-39.4 ng/mL | 7-13 years | na | Two of the seven nested case-control studies found an inverse association between 25(OH) D levels and colo-rectal cancer risk and one found this association for colon-cancer (trend analysis). The chort study found inverse association between 25(OH)D and colon-rectal cancer mortality (trend analysis). In the meta-analysis, OR for CRC by 20ng/mL was 0.57 (0.43-0.76). For colon and rectal cancer the associations were not statistically significant in the meta-analysis. | The authors conclusion was that the results supports that serum 25(OH)D is inversely related to CRC risk. |
| Summary table 12 Colon/ Colorectal cancer | | | | | | | | | | | |
| WCRF 2007 (50) | SLR - report | Eleven cohort studies and 17 case-control studies investigated total vitamin D and/or dietary vitamin D and colorectal cancer. Four cohort studies investigated plasma or serum vitamin D. | *Summary on Dietary vitamin D*:  Twelve estimates from 11 cohort studies reported analyses of the highest intake groups compared to the lowest. Six of these showed non-significant decreased risk , 2 studies reported no effect on risk; and 4 studies show non-significant increased risk. Meta-analysis was possible on 9 studies that investigated dietary vitamin D, giving a summary effect estimate of 0.99 (95% CI 0.97–1.00) per 100 IU/day, with moderate heterogeneity.  *Summary for serum/plasma vitamin D:* All four cohort studies showed non-significant decreased risk for the highest intake groups when compared to the lowest. Effect estimates were 0.73 (stated as non-significant); 0.4 (95% CI 1–1.4; serum 25-hydroxyvitamin D)and 1.1 (95% CI 0.4–3.2; serum 1,25 hydroxyvitamin D); 0.6 (95% CI 0.3–1.1; serum 25-hydroxyvitamin D) and 0.9 (95% CI 0.5–1.7; serum 1,25 hydroxyvitamin D); and 0.53 (95% CI 0.27–1.04).  *Overall results:* The evidence on vitamin D was inconsistent. There is limited evidence suggesting that foods containing vitamin D, or better vitamin D status, protect against colorectal cancer. | | | | | | | | |

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| Summary table 13. Breast cancer | | | | | | | | | |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Cacium intake | S-25OHD | Follow-up time | Dietary intake estimation | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Chung et al 2009 (28) | SLR-report | one chohort and two nested cace-control | alle age, and postmenopausal and premenopausal | women | na | no | less than 46 till above 120 nmol/l | 1mo till 12 years | na | HR for 25(OH) D levels below 63 nmol/l were 0.28 (0.08-0.93). Noen of the nested cace-control studies showed significant results. | Studies on vitamin D intake and risk of breast cancer were generally negative. Studies on 25(OH)D levels and breast cancer risk were very heterogeneous. Meta analysis showed a non significant protective effect on 25(OH)D levels in blood and breast cancer, but based on very heterogeneous results. |
| IARC 2008 (51) | SLR-report | The overall conclusion regarding breast cancer was that the epidemiological evidence from observational studies suggest an inverse association between serum 25-hydroxyvitamin D levels and the incidence of breast cancer, but the differences between studies are large, and the overall evidence is weak when case-control studies are not included in the meta-analysis. New cohort studies on serum 25-hydroxyvitamin D levels and breast cancer risk are warranted. | | | | | | | | | |
| WCRF 2007 (50) | SLR-report | For both post- and premenopausal breast cancer exposures like vitamin D, were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. | | | | | | | | | |

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| Summary table 14 Prostate Cancer | | |
| Reference | Study type | Overall results |
| WCRF 2007 (50) | SLR - report | Exposures like vitamin D, were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. |
| Chung et al 2009 (28) | SLR - report | Twelve nested case-control studies (three B, nine C) evaluated the association of baseline serum 25(OH)D concentrations and prostate cancer risk. No eligible RCTs were identified. Eight nested case-control studies found no statistically significant dose-response relationship between serum 25(OH)D concentrations and the risk of prostate cancer. One C-rated study found a significant association between lower baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and higher risk of prostate cancer. Another C-rated study suggested the possibility of an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer (i.e., lower and higher serum 25(OH)D concentrations were associated with an increased risk of prostate cancer compared to that of the in between reference level). |
| IARC 2008 (51) | SLR - report | The overall conclusion regarding prosate cancer was that observational studies have provided evidence of little or no effect of serum 25-hydroxyvitamin D on the incidence of prostate cancer. |

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| **Summary table 15 Diabetes type 1** | | |  |  |  |  |  |  |  |  |  |
| Ref-erence | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Cacium intake | S-25OHD | Follow-up time | Dietary intake estimation | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Zipitis Cand Akobeng 2008 (53) | SLR and meta analysis based on one cohort and 4 case control | 5 studies: one cohort and 4 case controls | up to 15 or up to 30 years | both | vitamin D supplements | no | na | not reported | na | Pooled odds ratio for taking supplements vs not OR=0.71, 95%CI 0.60-0.84, and in agreement with the cohort study i.e. RR for regular vs no supplements was 0.12(05% CI 0.03-0.51) and for irregular vs no supplementation 0.16 95% CI 0.04-074) | Supplementation with vitamin D in early childhood may offer protection against diabetes type 1 . RCTs are needed to establish causality. |

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| Summary table 16 Diabetes type 2 | | |  |  |  |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Cacium intake | S-25OHD | Follow-up time | Dietary intake estimation | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Pittas et al 2010 (55) | SLR of cohort studies and randomized trials | 4 cohorts in total 95 243 and 8 trials where 5 trials based on healthy population | 40-75 | both | 522 vs. 159 IU/D, >800 vs ≦200 IU/D, | na | Mean values: 75 vs 25 nmol/l, 61 vs 22 nmol/, 75 vs 22 nmol/l, and 61 vs 20 nmol/l | Cohorts: 9-20 years Trials: 2 monts - 7 years | Not reported | For men (Mini-Finland Health Survey) the association between higher vitamin D concentrations and lower risk of diabetes type 2 was significant, RR=017 (0.05-0.52) and in the Women's Health Cohort, RR=0.73 (0.54-0.99). None of the the other cohorts found significant results. Among 5 trials of participants with normal glucose tolerance at baseline, supplementations with vitamin D had no effect on fasting blood glucose level | The relationship between vitamin D and diabetes type 2 is uncertain |
| Parker et al 2010 (54) | SLR and meata-analysis | 2 cohort, 1 case-control, and 6 cross-sectional studies | mean age 40.5 -74.5 years | both | na | na | not reported | not reported | na | Seven of the 9 studies showed that high levels of vitamin D was associated with reduced level of diabetes. One study (cross-sectional) showed increased risk with increased levels of vitamin D. One study showed no effect. Pooled results demonstrated an overall decrease on the prevalence of diabetes associated with higher levels of vitamin D, OR 0.45 (95% CI 0.25-0.82) | High levels of vitamin D were associated with decreased risk of diabetes type 2. Further controlled trails are needed to evaluate causal associations |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Cacium intake | S-25OHD | Follow-up time | Dietary intake estimation | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Avenell et al 2009 (56) | RCT | 5292 participants | >69 years | both | 20 µg | 1000 mg calcium | na | 24-62 months | na | vitamin D vs placebo. Intention to treat analysis: OR=1.11 (0.77-1.62) Per protocol analysis OR=0.68 (0.40-1.16) | A large trial of daily 20 µg vitamin D and 1000 mg calcium in older people at high risk of another osteoporotic fracture did not suggest a protective effect against the development of type 2 diabetes or use of medications for type 2 diabetes. |

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| **Summary table 17. Vitamin D and body weight** | | | |  |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung et al 2007 (27) | SLR | Vitamin D alone vrs. placebo | Three RCTs, n= 178, 218, 100 | 21-71 yrs | both | 300 IU daily in one, 20000 or 40000 IU weekly in one and 20000 IU every second week in one | (or calcium to both groups) |  |  | no | No statistically significant effect |  |
|  |  | Vitamin D and calcium | Two RCTs (n=36000 postmenopausal women (WHI), n=63 overweight/obese premenopausal women) | 32-79 yrs | Women |  | 1000 mg or 1200 mg calcium |  | 7 yrs in WHI, 15 weeks in the smaller trial | no | A small stat. significant effect (0.13 kg)in the WHI trial, a larger effect (1 kg) which was not stat. significant in the small trial | The statistical sign. effect in WHI was not clinical significant |

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| **Summary table 18. Total mortality** | | |  |  |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Vestergaard et al 2009(36) | This is predominantly a review of reviews with no additional meta-analysis , confer Avenell below | |  |  |  |  |  |  |  |  |  |  |
| Avenell et al 2009 (35) | Cochrane review of randomized or quasi-randomized trials |  |  | Men over 65 years of age and post-menopausal women. | |  |  |  |  |  |  |  |
|  |  | Vitamin D or its analogues with or without calcium compared to placebo or calcium | 23 trials, 64,423 participants |  |  |  |  |  |  |  | 0.97, 95% CI 0.93 -1.01 |  |
|  |  | Vitamin D [D2, D3 or 25(OH)D] and calcium versus control or placebo | 14 trials, 54,203 persons |  |  |  |  |  |  |  | RR 0.94, 95%CI 0.89-0.99 |  |
| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung et al 2007 (27) | SLR | Vitamin D alone | 4 trials, 13,899 participants | mean age >70 years |  | 400 to 880 IU/d |  |  | 36-60 months |  | RR 0.97, 95%CI 0.92-1.02 | Vitamin D supplementation had no significant effect on all-cause mortality . Overall, data from four cohorts suggest no association between baseline 25(OH)D measurements and total mortality, but one cohort reported a statistically significant inverse trend. |
|  |  | Vitamin D and calcium | 11 trials, 44,688 persons | > 50 years ? |  | 300 to 880 IU per day (most trials) | 500-1200 mg/day |  | 6 - 84 months (median 24 months) |  | RR0.93, 95 % CI 0.86 - 1.01 | No significant effect on all-cause mortality |

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| **Reference** | **Study type** |  | **Number of subjects/trials** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Bjelakovic et al. 2011 (57) |  |  |  |  |  |  |  |  |  |  |  | The analysis including all trials also included alfacalcidol and calcitriol and are not presented here |
|  | subanalysis | D3 single |  |  |  |  |  |  |  |  | RR 0.91 [ 0.82, 1.02 ] | Interaction between trial with and without calcium co-supplementation was not significant (p=0.67) |
|  |  | D3 + calcium |  |  |  |  |  |  |  |  | RR 0.95 [ 0.91, 0.99 ] |  |
|  |  | Vitamin D2 with or without calcium | 12 trials, 18349 participants |  |  |  |  |  |  |  | RR 1.02 (0.97-1.09) |  |
|  |  | Vitamin D2 alone |  |  |  |  |  |  |  |  | RR 1.04 (0.97-1.11) |  |
|  |  | Vitamin D2 + calcium |  |  |  |  |  |  |  |  | RR 1.00 (0.64-1.57) |  |

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| **Table 19 Hypertension and blood pressure** | | | |  |  |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Chung, et al. 2009(28) | SLR | Two nested case-control studies on 25OHD and hypertension and three trials on vitamin D supplements and blood pressure | Adults and elderly | Both sexes | Not assessed, trials on vitamin D supplements | Not included | In nested case control studies only: From less than 37.5 nmol/L to over 80 nmol/L | Four, seven and eight years in nested case controls | na | **Hypertension**: a combined nested case-control study of men from HPFS and women from NHS showed a five fold incidence of hypertension in men after 4 and 8 years who had 25(OH)D under 37.5 nmol/L at baseline compared with those above 37.5, and sixfold higher than those above 75 nmol/L. Women with 25(OH)D below 37.5 at baseline had also higher incidence of hypertension after 4 years but not 8 years. A nested case-control study from the NHS2 showed that after 7 years women in the three quartiles with baseline values below 80.5 nmol/L were 50-60% more likely to develop hypertension than those in the highest quartile.**Blood pressure**:three trials, with different doses of vitamin D (800 IU daily, a single dose of 100,000 IU or 120,000 IU every two weeks) compared with placebo. None of the studies reported significant differences in diastolic blood pressure, while systolic blood pressure was decresed by 6 mmHg in one study of older women who received both 800 IU vitamin D and Calcium compared with Calcium alone. | No general conclusions in paper |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Jorde et al. 2010 (61) | Double blind RCT | 438 indiv | 2 -70 yrs | Both sexes | DD group 40000IU/wk, DP group 20000IU/wk, PP group placebo | not reported | DD: 140.0 nmol/L (34.7), DP:101.0 nmol/L (21.0), PP: 59.0 nmol/L (20.6) | 12 months | no | No difference between the 3 groups for serum lipids: Total cholesterol, TG, HDL chol, LDL chol, Apo A1, Apo B. No significant differences in delta values for glucose. Slight but signifant increase in systolic BP in DP group | Findings do not support a positive effect of vitamin D supplements on glucose tolerance, blood pressure or lipid profile and do not help in explaining the association between low 25(OH)D and CVD and mortality |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Pittas et al 2010 (55) | Systematic review of controlled trials and longitudinal observation studies | Three studies from 4 cohorts reported on hypertension and vitamin D, including 32 181 subjects. Ten trials on vitamin D supplementation and blood pressure. Trials total nr individuals 37162, with Women´s Health Initiative study contributing 36 282. | Adults and elderly | Both sexes | Vitamin D supplements from 400 to 8571 IU/day in trials. In WHI trial 400 IU/day combined with CalciumNot reported for longitudinal studies | Ca supplements combined with vitamin D in some studies, including the largest one, Women´s Health Initiative | Baseline levels not reported | Longitudinal studies up to 8 years. Trials from 5 weeks to 7 years in Women's Health Initiative trial | no | In three cohorts there was a significant association between low 25(OH)D and higher incidence of hypertenstion. In one study association after 4 yrs for men: RR=6.13 (CI 1.00-37.8) and 8 yrs 3.53 (CI 1.02, 12.3). For women 4 yrs RR=2.67 (CI 1.05, 6.79) 8 yrs 1.70 (CI 0.92, 3.16), comparing <37.5 nmol/L 25(OH)D with risk of hypertension. No significant effects found in trials, including the WHI trial. | Lower 25(OH)D concentration or vitamin D intake may be associated with higher risk for incident hypertension. Trials as a whole do not show statistical significant effects of vitamin D supplementation on blood pressure. |

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| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Witham et al 2009 (59) | Systematic review of RCTs | Eleven RCTs, only three of which used unactivated vitamin D as supplement in healthy adults. Other studies were on heart patients and/or using activated vitamin D. Number of subjects varied from 18 to 145 | Adults and elderly. Mean age varied from 48 to 75. | Both sexes | Only vitamin D supplements, ranging from 200-800 IU/day | Not reported. Ca supplements combined with vit D in two studies (Pfeifer 2001, Schleithoff 200-5 | Baseline levels 25nmol/L to 63nmol/L | 5 weeks to 12 months | na | Two of the three studies were also included in Chung et al 2009. The additional study (Pan et al) was on elderly women in Taiwan receiving 200 IU for 11 weeks. In the three studies with normotensive subjects at baseline , there was no effect on blood pressure with intervention. Overall reduction in systolic BP in all studies was -6.2mmHg (95% -12.3 to -0.04, p=0.05). Diastolic BP change was insignificant. | vitamin D might have a small beneficial effect on hypertensive patients, by lowering systolic blood pressure, but not in normotensives. |
| Wu SH et al 2010(60) | Review and Meta analysis of double-blind RCTs of oral vit D supplements | Four studies including 429 participants. | Adults and elderly | Both sexes | Vitamin D supplements 5 µg/day , 10 µg/day or single dose 2.5 mg | Ca supplements, 600mg or 1200 mg/day given in three of the four studies | Not reported | 5 to 15 weeks | not reported | Three of the four studies are included in Witham 2009 study. The additional study is by Major 2007 and includes 33 women, followed for 15 weeks. Weighted mean difference in systolic blood pressure was -2.44 95% CI -4.86, 0.02, and for diastolic pressure -0.02 95%CI -2.19,1.94) | Oral vitamin D may reduce systolic blood pressure. Evidence is week due to small number of trials. |

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| Table 20. Cardiovascular disease end point | | | | | | |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | 25(OH)D | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Chung, M. et al 2009 (28) | SLR | One RCT with 2700 subjects and four cohort studies | RCT: elderly (68-85 yrs), cohort studies: one study, 51-70 yrs, 3 studies, >70 yrs: 2 studies | Both sexes | RCT: 100000IU/4months,not reported for cohort studies | RCT: 742mg/day Calcium | <37.5nmol/L to >75nmol/L | RCT:5 yrs, cohort studies: 10 yrs (Giovannucci and Marinemi), Wang 5.4 yrs, Melamed 8.7 yrs. | NA | **RCT**: N=1345 intervention, after 4 years, no significant effects of vit D suppl.on incidence or mortality from various cardiovascular outcomescompared with placebo . **Cohort studies**: 2 studies found significant associations: Wang 2008: OR 1.70, 95% CI 1.08, 2.67 for 25(OH)D <37.5nmol/L, Giovannucci 2208 OR=2.09, 95% CI 1.24,3.54 for 25(OH)D < 37.5 nmolL, Melamed 2008, found no significant associations between 25(OH)D <44.5nmol/L and cardiovascular death OR=1.2 95%CI 0.87, 1.64. Marniemi 2005 no association between 25(OH)D and cardiovascular infarction in 755 elderly Finnish men and women. | Data are inconclusive: The single RCT does not find an effect of vitamin D supplementation in elderly British population on cerebrovascular death outcome. In cohort studies significant associations are found between progressively lower 25(OH)D concentrations and progressively increased risk of cardiovascular disease in two studies of people 40-75 years old but no associations found in one study. |

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| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **25(OH)D** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Grandi, et al 2010 (62). | systematic review of prospective studies | 9 studies, 4 on incidence, 5 on mortality | Mean age from 44.8 to 78.6 | Both sexes | not reported | not reported | 7.6ng/L->30ng/L | 5-27.1 yr | na | **Incidence studies** (Marinemi 2005, Giovannucci 2008, Wang 2008 and Bolland 2010). Fatal and nonfatal events: RR significantly increased with lower 25(OH)D in two studies (Giovannucci and Wang), not Marinemi and Bolland. **Mortality studies, cardiovascular deaths (highest vs. lowerst 25(OH)D quartiles or quintiles**: Dobnig RR= 2.22 (1.57, 3.13); Melamed RR= 0.89; Pilz 2009 RR= 1.22 (O.9-1.65); Kilkkinen 2009 RR= 0.91 (0.70-1.18); Semba 2010 RR= 2.64 (1.14-4.79) | Overall the published data seem to be in favor of an inverse association between 25(OH)D and CVD risk. However, given the heterogeneity of eligible studies in terms of study population, outcome and exposure levels, there remains a need for additional large scale studies to further elucidate the role of vit D as a potential modifiable risk factor for CVD |
| Parker et al 2010 (54) | Systematic review and meta-analysis. Outcomes: CVD (including myocardial infarction, stroke and periferal disease). Metabolic syndrome and DM | 28 studies, 5 cohort, 3 case-control, 20 cross sectional, including 99,745 participants | Mean age from 40.5-74.5 yrs | Both sexes | not reported | Calcium intake adjusted for in some studies | yes | not reported | No | High levels of 25(OH)D associated with lower prevalence of cardiometabolic disorders OR= 0.57 (95%CI 0.48-0.68) in meta analysis. All 7 cohort studies supported association between cardiometabolic disease and high 25(OH)D, OR=0.42 (95%CI 0.28-0.65). Two of three case control studies and 19 of 23 cross sectional studies supported the association. One case control study showed the opposite effect. By outcome: CVD: OR= 0.67 (0.55,0.81). Metabolic syndrome:OR= 0.59 (0.38,0.64). DM: OR=0.45 (0.25,0.82) | Further controlled trials are needed to evaluate causal association between cardiometabolic diseases and vitamin D levels. |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | 25(OH)D | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Pittas 2010(55) | Systematic review of cardiovascular disease outcomes | 9 cohort studies ( 43 527 participants in total) and 5 trials on vitamin D supplementation | adults and elderly | Both sexes | Not reportd | Combination vit D and Calcium in some studies | yes | Cohort studies: 5 to 27 years, trials follow up time 1,5 or 7 yrs. | na | None of the trials showed a significant effect of vitamin D supplementation on CVD outcomes. For longitudinal and observational cohort studies, 5 of 9 analysis showed an association between lower 25(OH)D and increased CVD risk | Lower 25(OH)D may be associated with higher risk for cardiovascular disease. |
| Wang et al 2010 (63) | Systematic review of vitamin D supplementation | 6 cohort studies, 2 RCT with vit D alone, 2 RCT with combination vit D and Calcium | Adults and elderly | Both sexes | Dietary intake assessed in only one study, supplements in others | Calcium supplement use in some studies | Not reported | not reported | na | Five of the six trials were on patients on hemodialysis, and all of these showed lower risk of CVD in those receiving vitamin D. Only one prospective study, that of Bostic et al was on the general population. Supplemental intake greater that 400 IU was associated with lower risk of CVD mortality RR= 0.80 (CI 0.57-1.13). | Limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk. |

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| **Summary table 21. Infection end points** | | | |  |  |  |  |  |  |  |  |
| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **Vitamin D intake** | **Calcium intake** | **S-25OHD** | **Follow-up time** | **Dietary intake** | **RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc.** | **Overall results** |
| Chung et al 2009(28) | Systematic review | One study on infectious disease mortality reviewed, cohort | Adults | Male/female | Not reported | Not reported | Quartiles ranging from <44nmol/l to >80 nmol/l | 7-8 yrs | Not reported | Risk estimates not reported | No effect on infectious disease mortality. Study rated C |
| Nnoaham and Clarke 2008 (65) | Systematic review of prospective and case control studies | Seven studies, 3 prospective, 4 case-control, on association between low serum vitamin D and risk of active tuberculosis | Adults, mostly non-European populations | Male/female | Not reported | Not reported | Median ranges from 16 nmol to 145 nmol/l. | Not reported | Not reported | Effect size, meta analysis = 0.68; 95% CI 0.43, 0.93 | Low serum vitamin D levels are associated with active tuberculosis. |
| Urashima et al 2010 (66) | Double blind randomized placebo controlled trial of vitamin D supplementation to prevent influenza A | 334 | Children aged 6-15 yrs | Male/female | 30 µg/day supplement to intervention group, dietary vitamin D not reported | Not reported | Not measured |  | Not reported | Relative risks for influenza A = 0.58; 95% CI 0.34, 0.99 | Study suggests that supplementation of vitamin D may reduce incidence of influenza A in schoolchildren |

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| Reference | Study type | Number of subjects/studies | Age | Sex | Vitamin D intake | Calcium intake | S-25OHD | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Yamshchikov et al 2009 (64) | Systematic review of clinical trials | 13 studies, 10 of these were placebo controlled | Adults and children | Male/female | Vitamin D supplements ranging from 10 µg/d to 2500 µg bimonthly | Not reported | Baseline and follow-up values reported in six of the 13 trials | From 12 months to 20 yrs | Not reported | Risk estimates not reported | Need for more research to evaluate effects of vitamin D supplementation on overall mortality and also into adjunctive therapy for vitamin D on tuberculosis, influenza and viral upper respiratory diseases |

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| **Summary table 22. Effect of UV exposure on S-25(OH)D** | | | | | | | | | | |  | |  |  |  |
| **Reference** | **Study type** | **Number of subjects/studies** | **Age** | **Sex** | **UV-exposure** | **Vitamin D intake** | **Calcium intake** | **S-25OHD baseline** | **S-25OHD final** | **S-25OHD increment** | **Methods** | **Season/ location** | | **Duration of intervention** | **Overall results** |
| Cranney et al 2007 (27) | SLR of RCTs | Eight RCTs (N = 337) | adults; elderly; one in infants | mixed | Solar exposure: 4 RCTs; 4 artifical UV- exposure. Skin type was reported in 2 RCts. Exposure : one single exposure to 3 times a week, ten times over 12 days, daily. Comparators: placebo; vitamin D3 supplementation; lower energy UV-B +/- 50 000 IU vitamin D2 vs vitamin D2 alone. | Dietary vitamin D intake (incl. Supplements) was reported in one trial. | calcium intake was reported in one study | Yes | Yes | Yes | RIA, HPLC, CBPA | | Reported in some | 3 day s to 7 months | Both artificial and solar exposure increased serum 25(OH)D concentrations in vitamin D deficient and replete subjects. Three trials in elderly nursing home populations (solar or artificial UV-B exposure) demonstrated significant increases in serum 25(OH)D concentrations. One trial using artificial UV-B exposure in elderly females reported an increase of 42 nmol/L in serum 25(OH)D (measured by RIA) with ½ MED exposure to the lower back, three times per week. These results support the belief that older individuals have adequate capacity to synthesize vitamin D3 in response to UV-B exposure, despite the decreased availability of 7- dehydrocholesterol in the skin. One trial evaluated the effect of sunscreen on serum 25(OH)D concentrations and found that the UV-B response was not suppressed by sunscreen use. There is fair evidence that solar and artificial UV-B exposure increase 25(OH)D levels. The included trials did not address the issue of whether serum 25(OH)D response is attenuated in heavily pigmented groups. It was also not possible, to evaluate the impact of effect modifiers such as age, ethnicity, seasonality and latitude. |

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| Summary table 23. Upper tolerable intake - safety outcomes in RCTs | | | | | | | |  |  |  |  |  |  |
| Reference | Study type | Number of subjects/studies | Age | Sex | Outcomes | Vitamin D supplementation | Calcium supplementation | S-25OHD | S-25(OHD assay | Follow-up time | Dietary intake | RESULTS: effect, mean, SD, N (per group), RR/OR/HR confidence interval etc. | Overall results |
| Cranney et al 2007 (27) | SLR of RCts | 22 RCTs( 47 802 subjects) | infants, adults, elderly | mixed | S-calcium; hypercalcuria; renal stones; death in 11 trials, others | 19 RCTs: vitamin D 3; 3 RCTs vitamin D2; 7 RCTs had one or more doses; 15 had one or more arms if vitamin D with calcium. Comparators: 12 trails placebo, 5 calcium, 6 another does of vitamin D | Included in 15 trials | Yes | CPBA, RIA, HPLC, chemiluminiscence | 12 weeks to 7 years | ND | 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 size and had short durations of exposure to vitamin D. Event rates were low across trials in both the treatment and placebo arms. The WHI trial on women aged 50 to 79 years, examined the effect of vitamin D3 400 IU (the daily reference intake for women aged 50 to 70 years and below the 600 IU reference intake for women > 70 years) in combination with 1,000 mg calcium carbonate versus placebo and found an increase in the risk of renal stones (Hazard Ratio 1.17 95% CI 1.02-1.34), corresponding to 5.7 events per 10,000 person years of exposure. | There is fair evidence that vitamin D supplementation above current reference intakes, with or without calcium supplementation, was well tolerated. A significant increase in kidney stones was observed in one large trial in postmenopausal women taking 400 IU vitamin D3 with calcium. The quality of reporting of toxicity outcomes was inadequate in a number of the trials, and most trials were not adequately powered to detect adverse events. |

NNR5 – Excluded articles for vitamin D- First search

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| **Article** | **Reason for exclusion** |
| (2006). "NIH State-of-the-Science Conference Statement on Multivitamin/Mineral Supplements and Chronic Disease Prevention." NIH Consens State Sci Statements **23**(2): 1-30. | building on a review of reviews. Pointing to Cranney et al (2007) |
| Annweiler, C., et al. (2009). "Vitamin D and cognitive performance in adults: a systematic review." Eur J Neurol **16**(10): 1083-1089. | Not a study question |
| Annweiler, C., A. M. Schott, et al. (2009). "Vitamin D-related changes in physical performance: a systematic review." The journal of nutrition, health & aging **13**(10): 893-898. | Not a study question |
| Autier, P., et al. (2007). "Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials." Arch Intern Med **167**(16): 1730-1737. | INCLUDED in Chung et al(2009) |
| Bergman, G. J., et al. (2010). "Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis." Current medical research and opinion **26**(5): 1193-1201. | Not SLR (meta analysis) |
| Bischoff-Ferrari, H. A., et al. (2009). "Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials." BMJ **339**: b3692. | Not SLR (meta analysis) |
| Bischoff-Ferrari, H. A., et al. (2004). "Effect of Vitamin D on falls: a meta-analysis." JAMA **291**(16): 1999-2006. | Incl. in Cranney et al (2007) |
| Bischoff-Ferrari, H. A., et al. (2005). "Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials." JAMA **293**(18): 2257-2264. | Not SLR (meta analysis) |
| Bischoff-Ferrari, H. A., et al. (2009). "Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials." Arch Intern Med **169**(6): 551-561. | INCLUDED in Vestergaard et al 2010 |
| Boonen, S., et al. (2007). "Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative metaanalysis of randomized controlled trials." J Clin Endocrinol Metab **92**(4): 1415-1423. | Not SLR (meta analysis) |
| Chen, P., et al. (2010). "Meta-analysis of vitamin D, calcium and the prevention of breast cancer." Breast cancer research and treatment **121**(2): 469-477. | Not SLR |
| Gandini, S., et al. (2010). "Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma." Int J Cancer. | Not SLR (meta analysis) |
| Gandini, S., et al. (2009). "Vitamin D and skin cancer: a meta-analysis." Eur J Cancer **45**(4): 634-641. | Not a study question |
| Gaugris, S., et al. (2005). "Vitamin D inadequacy among post-menopausal women: a systematic review." QJM **98**(9): 667-676. | Not a study question |
| Gillespie, L. D., et al. (2003). "WITHDRAWN: Interventions for preventing falls in elderly people." Cochrane Database Syst Rev(4): CD000340. | Withdrawn, see Gillespie et al (2009) and Cameron et al(2010) |
| Gissel, T., et al. (2008). "Intake of vitamin D and risk of breast cancer--a meta-analysis." J Steroid Biochem Mol Biol **111**(3-5): 195-199. | Not SLR |
| Gorham, E. D., et al. (2007). "Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis." Am J Prev Med **32**(3): 210-216. | Not SLR (meta analysis) |
| Hagenau, T., et al. (2009). "Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis." Osteoporos Int **20**(1): 133-140. | Not SLR |
| Huncharek, M., et al. (2008). "Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies." Nutrition and Cancer **60**(4): 421-441. | Not SLR (meta analysis) |
| Huncharek, M., et al. (2009). "Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies." Nutr Cancer **61**(1): 47-69. | Not SLR (meta analysis) |
| Izaks, G. J. (2007). "Fracture prevention with vitamin D supplementation: considering the inconsistent results." BMC Musculoskelet Disord **8**: 26. | Not SLR |
| Jackson, C., et al. (2007). "The effect of cholecalciferol (vitamin D3) on the risk of fall and fracture: a meta-analysis." QJM **100**(4): 185-192. | Not SLR (meta analysis) |
| Kinney, D. K., et al. (2009). "Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: a role for prenatal vitamin d deficiency and infections?" Schizophr Bull **35**(3): 582-595. | Not a study question |
| Latham, N. K., et al. (2003). "Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: a systematic review." J Am Geriatr Soc **51**(9): 1219-1226. | Not SLR (meta analysis) |
| Mahomed, K., et al. (2000). "Vitamin D supplementation in pregnancy." Cochrane Database Syst Rev(2): CD000228. | WITHDRAWN 2010 |
| McCullough, M. L., et al. (2008). "Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature." Preventive medicine **46**(4): 298-302. | Part of World Cancer Research Fund report |
| Mimouni, F. B., et al. (2009). "Vitamin D requirements in the first year of life." Curr Opin Clin Nutr Metab Care **12**(3): 287-292. | Not SLR |
| Mosekilde, L., et al. (2007). "Fracture prevention in postmenopausal women." Clin Evid (Online) **2007**. | INCLUDED as Vestergaard et al (2010) |
| Papadimitropoulos, E., et al. (2002). "Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women." Endocrine reviews **23**(4): 560-569. | Not SLR (meta analysis) |
| Pilz, S., et al. (2009). "Vitamin D status and arterial hypertension: a systematic review." Nature reviews. Cardiology **6**(10): 621-630. | Not SLR |
| Pittas, A. G., et al. (2007). "The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis." The Journal of clinical endocrinology and metabolism **92**(6): 2017-2029. | Not SLR |
| Rhee, H. V., J. W. Coebergh, et al. (2009). "Sunlight, vitamin D and the prevention of cancer: a systematic review of epidemiological studies." European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). | Not a SLR |
| Richy, F., et al. (2008). "Differential effects of D-hormone analogs and native vitamin D on the risk of falls: a comparative meta-analysis." Calcif Tissue Int **82**(2): 102-107. | Not SLR (meta analysis) |
| Richy, F., et al. (2005). "Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: a comparative meta-analysis." Calcif Tissue Int **76**(3): 176-186. | Not SLR (meta analysis) |
| Stransky, M., et al. (2009). "Nutrition as prevention and treatment of osteoporosis." Physiol Res **58 Suppl 1**: S7-S11. | Not SLR |
| Tang, B. M., et al. (2007). "Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis." Lancet **370**(9588): 657-666. | Not a study question |
| Thacher, T. D., et al. (2006). "Nutritional rickets around the world: causes and future directions." Ann Trop Paediatr **26**(1): 1-16. | Not a study question |
| Weatherall, M. (2000). "A meta-analysis of 25 hydroxyvitamin D in older people with fracture of the proximal femur." N Z Med J **113**(1108): 137-140. | Not SLR |
| Wei, M. Y., et al. (2008). "Vitamin D and prevention of colorectal adenoma: a meta-analysis." Cancer Epidemiol Biomarkers Prev **17**(11): 2958-2969. | Meta-analysis |
| Yin, L., et al. (2009). "Meta-analysis of longitudinal studies: Serum vitamin D and prostate cancer risk." Cancer Epidemiol **33**(6): 435-445. | Not SLR (meta analysis) |
| Zhao, Z. Z., et al. (2009). "[Meta-analysis of relationship of vitamin D receptor gene polymorphism and tuberculosis susceptibility]." Zhonghua Jie He He Hu Xi Za Zhi **32**(10): 748-751. | Not a study question |
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NNR5 – Excluded articles for vitamin D- Second search

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| **Article** | **Reason for exclusion** |
| Annweiler, C., et al. (2009). "Vitamin D-related changes in physical performance: a systematic review." The journal of nutrition, health & aging **13**(10): 893-898. | Included in first search |
| Bacon, C. J., et al. (2009). "High-dose oral vitamin D3 supplementation in the elderly." Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA **20**(8): 1407-1415. | Patients |
| Bartley, J. (2010). "Vitamin D, innate immunity and upper respiratory tract infection." The Journal of laryngology and otology **124**(5): 465-469. | Not SLR |
| Biancuzzo, R. M., et al. (2010). "Fortification of orange juice with vitamin D(2) or vitamin D(3) is as effective as an oral supplement in maintaining vitamin D status in adults." The American journal of clinical nutrition **91**(6): 1621-1626. | Included in snowball Black et al(2012) |
| Binkley, N. (2009). "Is vitamin D the fountain of youth?" Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **15**(6): 590-596. | Not SLR |
| Cameron, I. D., et al. (2010). "Interventions for preventing falls in older people in nursing care facilities and hospitals." Cochrane database of systematic reviews (Online)(1): CD005465. | Already included as a new version of withdrawn paper(Gillespie) in first search |
| Cashman, K. D., et al. (2009). "Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age." The American journal of clinical nutrition **89**(5): 1366-1374. | Included in snowball Cashman et al (2011) |
| Cooper, K., et al. (2010). "Chemoprevention of colorectal cancer: systematic review and economic evaluation." Health technology assessment (Winchester, England) **14**(32): 1-206. | Not SLR; Chemoprevention |
| Cook, L. S., H. K. Neilson, et al. (2010). "A systematic literature review of vitamin D and ovarian cancer." American journal of obstetrics and gynecology **203**(1): 70 e71-78. | Not a study question |
| Egan, K. M. (2009). "Vitamin D and melanoma." Annals of epidemiology **19**(7): 455-461. | Not SLR |
| Hackman, K. L., et al. (2010). "Efficacy and safety of oral continuous low-dose versus short-term high-dose vitamin D: a prospective randomised trial conducted in a clinical setting." The Medical journal of Australia **192**(12): 686-689. | Very high doses, not relevant , patients |
| Janssen, H. C., et al. (2010). "Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation." Aging clinical and experimental research **22**(1): 78-84. | Patients |
| Kalyani, R. R., et al. (2010). "Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis." Journal of the American Geriatrics Society **58**(7): 1299-1310. | Already included in first search |
| Karkkainen, M. K., et al. (2010). "Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS)." Maturitas **65**(4): 359-365. | Included in snowball Murad et al(2011) |
| Khadilkar, A. V., et al. (2010). "Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls." Asia Pacific journal of clinical nutrition **19**(4): 465-472. | Not general population (underprivileged children from India) and not vitamin D alone (together with Ca):Asian population |
| Laaksi, I., et al. (2010). "Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men." The Journal of infectious diseases **202**(5): 809-814. | Endpoint not on our list (days absent from work due to acute repiratory tract infection): Not a study question |
| Li-Ng, M., et al. (2009). "A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections." Epidemiology and infection **137**(10): 1396-1404. | Included in Yamashchikov et al (2010) |
| Lips, P., et al. (2010). "Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency." The American journal of clinical nutrition **91**(4): 985-991. | Endpoint not on our list (body sway), not a study question |
| McCullough, M. L., et al. (2009). "Vitamin D status and impact of vitamin D3 and/or calcium supplementation in a randomized pilot study in the Southeastern United States." Journal of the American College of Nutrition **28**(6): 678-686. | Patients |
| Moreira-Pfrimer, L. D., et al. (2009). "Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial." Annals of nutrition & metabolism **54**(4): 291-300. | Effect of vit D + calcium on muscle strength in institutionalized elderly in Sao Paulo |
| Moschonis, G., et al. (2010). "The effects of a 30-month dietary intervention on bone mineral density: the Postmenopausal Health Study." The British journal of nutrition **104**(1): 100-107. | Mixed intervention |
| Nemerovski, C. W., et al. (2009). "Vitamin D and cardiovascular disease." Pharmacotherapy **29**(6): 691-708. | Not SLR |
| Pekkarinen, T., et al. (2010). "The same annual dose of 292000 IU of vitamin D (cholecalciferol) on either daily or four monthly basis for elderly women: 1-year comparative study of the effects on serum 25(OH)D concentrations and renal function." Clinical endocrinology **72**(4): 455-461. | I  Not a RCT |
| Pignotti, G. A., et al. (2010). "Is a lower dose of vitamin D supplementation enough to increase 25(OH)D status in a sunny country?" European journal of nutrition **49**(5): 277-283. | Not relevant. Effect of vit D suppl on 25OHD in osteoporotic patients in Sao Paulo |
| Pilz, S., et al. (2009). "Vitamin D status and arterial hypertension: a systematic review." Nature reviews. Cardiology **6**(10): 621-630. | not SLR |
| Robison, R., et al. (2010). "The effect of prenatal and postnatal dietary exposures on childhood development of atopic disease." Current opinion in allergy and clinical immunology **10**(2): 139-144. | Not a study question; not SLR |
| Sahu, M., et al. (2009). "Vitamin D replacement in pregnant women in rural north India: a pilot study." European journal of clinical nutrition **63**(9): 1157-1159. | Not SLR; Asian population |
| Sanders, K. M., et al. (2010). "Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial." JAMA : the journal of the American Medical Association **303**(18): 1815-1822. | Included in Vestergaard et al 2010; Murad et al 2011 |
| Seamans, K. M., et al. (2010). "Cholecalciferol supplementation throughout winter does not affect markers of bone turnover in healthy young and elderly adults." The Journal of nutrition **140**(3): 454-460. | Not a study question |
| Siafarikas, A., et al. (2011). "Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants." Archives of disease in childhood **96**(1): 91-95. | Not a RCT |
| Stephenson, D. W., et al. (2009). "The lack of vitamin D toxicity with megadose of daily ergocalciferol (D2) therapy: a case report and literature review." Southern medical journal **102**(7): 765-768. | Not SLR |
| Ukinc, K. (2009). "Severe osteomalacia presenting with multiple vertebral fractures: a case report and review of the literature." Endocrine **36**(1): 30-36. | not SLR |
| Ward, K. A., et al. (2010). "A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females." The Journal of clinical endocrinology and metabolism **95**(10): 4643-4651. | Dosing 4 times per year, not relevant |
| Wejse, C., et al. (2009). "Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial." American journal of respiratory and critical care medicine **179**(9): 843-850. | Patients |
| Witham, M. D., et al. (2009). "Effect of vitamin D on blood pressure: a systematic review and meta-analysis." Journal of hypertension **27**(10): 1948-1954. | Already included in first round |
| Yamshchikov, A. V., et al. (2009). "Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials." Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists **15**(5): 438-449. | Already included in first round |
| Zhou, G., et al. (2009). "Optimizing vitamin D status to reduce colorectal cancer risk: an evidentiary review." Clinical journal of oncology nursing **13**(4): E3-E17. | Not a study question |
| Zhu, K., et al. (2010). "A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency." Journal of the American Geriatrics Society **58**(11): 2063-2068. | Included in snowball Muir et al 2011 |
| Yin, L., N. Grandi, et al. (2010). "Meta-analysis: serum vitamin D and breast cancer risk." European journal of cancer (Oxford, England : 1990) **46**(12): 2196-2205. | Not a SLR |