APPENDICES

1. Documentation of vitamin D search
2. Evidence tables
3. Summary tables
4. List of excluded studies

Appendix 1. Documentation of vitamin D search

1.1 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])

1.2 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])

1.3 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])

1.4 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])

1.5 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])

1.6 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])

1.7 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])

1.8 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])

1.9 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])

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

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

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	

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

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

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

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

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

Appendix 3 table 1

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).

Appendix 3 table 1

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

Appendix 3 table 2

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.

Appendix 3 table 2

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).

Appendix 3 table 2

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.

Appendix 3 table 2

		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.

Appendix 3 table 2

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 º 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.

Appendix 3 table 2

Appendix 3 table 3

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.

Appendix 3 table 4

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)	

Appendix 3 table 5

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

Appendix 3 table 5

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

Appendix 3 table 6

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'	

Appendix 3 table 6

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?											

Appendix 3 table 6

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)

Appendix 3 table 6

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)

Appendix 3 table 6

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		

Appendix 3 table 6

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.		

Appendix 3 table 7

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

Appendix 3 table 7

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

Appendix 3 table 7

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'

Appendix 3 table 7

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.'

Appendix 3 table 7

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

Appendix 3 table 8

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

Appendix 3 table 9

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

Appendix 3 table 9

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

Appendix 3 table 9

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

Appendix 3 table 9

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.

Appendix 3 table 9

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.

Appendix 3 table 10

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.

Appendix 3 table 10

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.

Appendix 3: Table 11

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.

Appendix 3: Table 11

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*
IARC 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

Appendix 3: Table 12

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.

Appendix 3: Table 12

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.

Appendix 3: Table 13

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 postmen opausal and premeno pausal	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.									

Appendix 3: Table 14

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.

Appendix 3: Table 15

Summary table 15 Diabetes type 1											
Ref-erence	Study type	Number of subjects/studies	Age	Sex	Vitamin D intake	Caciu m 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.

Appendix 3: Table 17

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

Appendix 3: Table 17

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 calciu m	na	24-62 months	na	vitamin D vsplacebo. 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.

Appendix 3 table 17

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

Appendix 3 table 17

Appendix 3 table 18

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	

Appendix 3 table 18

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

Appendix 3 table 18

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)	

Appendix 3 table 19

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

Appendix 3 table 19

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

Appendix 3 table 19

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.

Appendix 3 table 19

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.

Appendix 3 table 20

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.

Appendix 3 table 20

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.

Appendix 3 table 20

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.

Appendix 3 table 21

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

Appendix 3 table 21

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

Appendix 3 table 22

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.

Appendix 3 table 23

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

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

NNR5 – Excluded articles for vitamin D- Second search

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

Appendix 4 List of excluded studies

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

Appendix 4 List of excluded studies

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