

# Effects of Different Doses of Vitamin D Replacement in Middle Eastern and North African Population: a Systematic Review and Meta-analysis.

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## Abstract:

### *Background:*

Countries in the Middle East and North Africa (MENA) register some of lowest vitamin D levels worldwide. Yet, the optimal dose of vitamin D required to reach desirable serum 25-hydroxyvitamin D (25(OH)D) levels in populations from this region is unknown.

### *Objectives:*

The main objective is to define the mean 25(OH)D level reached with low (<800IU), moderate (800-2,000IU) or high (>2,000 IU) daily dose of vitamin D in subjects in the MENA countries, by age and reproductive status. We will also deduce the mean serum 25(OH)D level reached by 97.5% of individuals in above treatment groups, as well as the proportion of subjects who reach a mean 25(OH) D level  $\geq 20$  ng/ml in the three above treatment groups.

Other outcomes investigated are fracture rate, fall and imbalance rate, kidney stones rate, hypercalcemia-hypercalciuria, hyperparathyroidism, metabolic parameters (diabetes and lipids), bone mineral density, muscle strength, mortality.

### *Materials and methods:*

#### *Data sources:*

A search for English and Non-English articles will be done using Medline, PubMed, the Cochrane Controlled Trials Register, EMBASE, Popline and Index Medicus and Global Health Library without any time restriction. We will also search ClinicalTrial.gov and the WHO International Clinical Trials Registry (ICTRP) to try to retrieve unpublished or preliminary data by directly contacting the authors. In addition, references listed in recently published reviews will be screened. Vitamin D experts will be also contacted.

#### *Study selection:*

Only randomized controlled trials of oral vitamin D supplementation (cholecalciferol, ergocalciferol) with or without calcium supplementation, versus calcium supplementation or placebo, or those comparing different doses of vitamin D, conducted on community dwelling individuals in MENA countries, will be included.

#### *Data Extraction:*

Duplicate and independent data extraction will be done using predefined data fields, including study quality indicators. Discrepancies will be solved by discussion, and when unsuccessful by an expert author.

*Risk of bias:*

Risk of bias assessment will be done on all included studies, by 2 reviewers in duplicate and independently, using the Cochrane Collaboration's Risk of Bias tool 2011.

*Summary measures:*

Continuous outcomes will be expressed as mean differences (MD) with 95% confidence interval (CI). Dichotomous outcomes will be expressed as risk ratio (RR) and hazard ratio (HR) with 95% CI.

*Primary analysis and additional analysis:*

The primary analysis will be done using a random-effects model.

Additional pre-specified subgroup analysis and sensitivity analysis will be done according to gender, type of vitamin D (D2 or D3), vitamin D assay, use or not of calcium supplementation and BMI. Sensitivity analysis, if applicable, will be done, restricting the analysis to published trials, MENA individuals living in MENA countries exclusively and trials with mean baseline 25(OH)D  $\leq$  20ng/ml.

*Risk of bias across the studies:*

Publication bias and bias due to selective outcome reporting will be assessed using a funnel plot and Egger's test.

## **Effects of Different Doses of Vitamin D Replacement in Middle Eastern and North African Population: a Systematic Review and Meta-analysis.**

### **INTRODUCTION:**

Hypovitaminosis D is a worldwide problem (1, 2). Low 25(OH)D levels, defined as <20ng/ml, are prevalent in developing countries, especially in the Middle East, South Asia and Sub Saharan Africa (2, 3). In the Middle East and North Africa (MENA) region, in addition to advancing age and female gender, similar to other countries, specific risk factors in adults include multiparity, clothing style, season, socio-economic status and urban living (4). Prolonged breast feeding without adequate supplementation is a major predictor of hypovitaminosis D in infants (4).

Vitamin D can be supplemented as ergocalciferol (D2) or cholecalciferol (D3). They differ by the composition of their side chain and may differ slightly in their effect on vitamin D status; the superiority of D3 in raising serum 25(OH)D levels, compared to D2, has been demonstrated in a recent meta-analysis by Tripkovic et al. (5). Enteral and parenteral preparations are available. The data on the difference between various dosing regimens on efficacy and safety is inconclusive (6-8). In one study comparing daily, weekly and monthly dosing frequencies in elderly following hip fracture, all doses have shown to be equally effective (9).

Vitamin D receptors are widespread in different tissues, explaining the different physiologic effects of vitamin D beyond the skeleton (10). Observational studies have associated hypovitaminosis D with increased risk of infections, cancer, auto-immune and cardio-vascular diseases (11). Meta-analysis of randomized controlled trials (RCTs) have shown that vitamin D supplementation improves multiple skeletal and possibly non-skeletal outcomes, including in adults a protective effect of vitamin D against falls (12) and fractures (13) and maybe decreased overall mortality (14), and in children improvement in BMD (15).

The latest Institute of Medicine (IOM) and Endocrine Society (ES) respective guidelines on vitamin D replacement in the general population, in 2010, were based on a systematic review of literature and defined the dietary requirements of vitamin D based on mineral and skeletal outcomes (16, 17). They did not target specifically MENA countries where 25(OH)D levels are lower compared to Western population (2). Furthermore, the ES guidelines have collected a wealth of RCTs conducted in each age category but suggested to use higher doses to reach their target of 25(OH)D level  $\geq 30$  ng/ml (16); doses that have been infrequently used in RCTs. IOM and ES differ in their recommendations in terms of target populations and desirable levels as well as other criteria used, and these are detailed in Appendices 1 and 2.

A previous systematic review by Autier et al. in 2012, assessed the influence of vitamin D supplementation on 25(OH)D level (18). However, this review targeted Caucasian population and only individuals above age 50 years; In addition, the authors did not systematically assess the risk of bias of the included trials. Similarly, Cashman et al. conducted a systematic review and meta-regression analysis of RCTs of vitamin D intake in 2011 to help define dietary intake recommendations in Europe. This review was limited to trials conducted in winter (minimal sun exposure), at latitudes higher than 40°S or 40°N and using vitamin D doses  $\leq 2000$  IU per day only and published before September 2007 (19). Another review that included all RCTs that used high doses of vitamin D revealed that these were

exclusively conducted in Caucasian subjects in western societies (11). Finally, a more recent meta-analysis, using the meta-regression method, found that higher increases in serum 25(OH)D occur with increasing age (>80 years), vitamin D dose (>800 IU daily), duration (>6 months) and decreasing baseline level (<50 nmol/l) (20).

Four recent meta-analyses failed to show a significant protective effect of vitamin D supplementation on multiple skeletal (adult BMD, hip fractures) and non-skeletal clinical outcomes (cancer, cardiovascular, diabetes and overall mortality) (21-24). However, these studies have multiple limitations. First, the change in 25(OH)D levels have not been consistently documented in the included trials, and if so, the mean 25(OH)D level achieved was between 50 and 70 nmol/l, implying that 50% of the study population reached levels that were below the above cut-offs and this may explain the absence of beneficial effect of vitamin D on various outcomes. Second, the duration of the studies may not have been long enough to allow for the beneficial effects of vitamin D supplementation to manifest (24). Third, some of the trials included in these meta-analyses (19, 22) used infrequent dosing (every 3, 6 or 12 months) with high dose of vitamin D supplementation; regimens that might not maintain steady 25(OH)D levels for the study duration (25). Interestingly, the study by Sanders et al., in a 3.5 years trial, revealed an increase in hip fracture risk using a single high dose of 500,000 IU once, higher risk in the first 3 months following the yearly dose administration (26). Conversely, an individual participant-level data meta-analysis revealed that vitamin D intake 800-2000 IU/day decreased the risk of both hip and vertebral fractures (13).

This review addresses the effect of vitamin D supplementation on serum 25(OH)D level in MENA population across all life cycle. It tries to evaluate the applicability of the IOM Recommended Daily Allowance (RDA) to subjects from MENA countries. The RDA for vitamin D, is by definition the vitamin D dose that would allow to  $\geq 97.5\%$  of participants to reach a desirable 25(OH)D level  $\geq 20$  ng/ml. The latter is a conservative desirable 25(OH)D level defined by IOM as one that has a beneficial effect on mineral metabolism at the population level.

## **2-OBJECTIVES:**

The main objective is to define the mean 25(OH)D level reached with low (<800IU), moderate (800-2,000IU) or high (>2,000 IU) daily dose of vitamin D in subjects in the MENA countries, by age and reproductive status.

We will also deduce the mean serum 25(OH)D level reached by 97.5% of individuals in above treatment groups, as well as the proportion of subjects who reach a mean 25(OH) D level  $\geq 20$  ng/ml in the three above treatment groups. This would allow validation of the applicability of the IOM to subjects in MENA countries.

Other outcomes investigated are fracture rate, fall and imbalance rate, kidney stones rate, hypercalcemia-hypercalciuria, hyperparathyroidism, metabolic parameters (diabetes and lipids), bone mineral density, muscle strength, mortality.

## **3-METHODS**

### **1-Eligibility criteria:**

a- *Type of studies:*

-*Inclusion criteria:*

- RCTs
- English and Non-English articles.
- Published and unpublished data.

We will try to get access to unpublished data of studies identified on trials registry through contact of authors.

- No publication date restriction.

-*Exclusion criteria:*

- Prospective interventional studies that are not randomized.
- Studies that did not report pre or post intervention 25(OH)D level.

In such a case, first we will try to contact the authors to get information about 25(OH)D level; If such information would not be available or we would not get any reply, the study will be excluded.

b- *Type of participants:*

-*Inclusion criteria:*

- Middle East and North Africa including the following countries: Algeria, Egypt, Libya, Morocco, Tunisia, Afghanistan, Bahrain, Iran, Iraq, Palestine/Israel, Syria, Lebanon, Kuwait, Yemen, Oman, Qatar, Saudi Arabia, Turkey, Jordan, United Arab Emirates.
- Apparently healthy, community dwelling individuals.
- Healthy individuals given vitamin D as a preventive measure of certain diseases or individuals with mild diseases that have no reason to have altered vitamin D metabolism.
- Both sexes.
- All age groups.
- Pregnant or lactating women.

-*Exclusion criteria:*

- Rickets in children and osteomalacia in adults characterized by low 25(OH)D, below 15 ng/ml with evidence of laboratory and radiologic abnormalities, as these individuals require higher doses of vitamin D supplementation (higher than the doses recommended for the general population).
- Institutionalized and hospitalized individuals; this would only apply to elderly and their needs are different. Public health guidelines should target the general population, not this unique subgroup.
- Individuals with chronic illnesses (chronic kidney disease (GFR  $\leq$ 30 ml/min), chronic advanced liver disease, heart failure (NYHA class  $\geq$  3)
- Individuals with conditions or on drug therapy that might affect vitamin D metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption, bypass surgery)

c- *Type of intervention:*

-*Inclusion criteria:*

-Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with or without calcium supplementation.

-*Exclusion criteria:*

-Studies that used synthetic or active vitamin D supplementation, as this type of supplementation is not recommended for the general population (16, 17).

-Studies that used vitamin D supplementation given intra-muscularly as the intra-muscular preparations have a more delayed peak in 25(OH)D level that can occur at 120 days (27).

-Studies that gave vitamin D supplementation for less than 3 months since 25(OH)D has a half-life of 2 weeks and at least 10 weeks are needed to reach a steady state (28).

-Studies that gave vitamin D supplementation spaced more than 1 month, given that 25(OH)D levels cannot be maintained with infrequent dosing (at intervals more than one month) (25, 29).

-Studies that used vitamin D supplementation as fortified food as the amount of vitamin cannot be defined accurately (30).

d- *Outcome measures:*

-*Primary outcome measures:*

Mean difference in serum 25(OH)D level reached and proportion of individuals who reach a 25(OH)D level  $\geq 20$  ng/ml between any two treatment arms, be it between vitamin D groups themselves (high dose versus low dose, high versus moderate dose, moderate dose versus low dose), or vitamin D groups and placebo, in each age category and reproductive status.

-*Secondary outcome measures:*

Comparing between the different treatment groups and in each age category:

-Incidence of hypercalciuria/hypercalcemia.

-Incidence of kidney stones.

-Incidence of hip fracture.

-Incidence of fall and imbalance.

-Serum calcium level.

-Urinary calcium level.

-Serum PTH level.

-Serum fasting blood glucose, glycosylated hemoglobinHbA1c, LDL, HDL, triglycerides (TG).

-Bone mineral density.

-Muscle strength and other muscle parameters.

-All cause mortality.

-Other adverse events (other than hypercalcemia, hypercalciuria, kidney stones, if present).

## **II-Information sources and search:**

Studies will be identified by searching electronic databases using the relevant Mesh Terms and keywords related to Vitamin D, MENA and RCTs. The search will be applied to Medline (1946 till present), Embase, PubMed and Cochrane Library without time or language limitation.

For full details of search strategy, see Appendix 3.

Similarly, the search will be done in Popline, Index Medicus and Global Health and in trials registries, ClinicalTrial.gov. and the WHO international Clinical Trials Registry (ICTRP).

The references lists of all systematic reviews of RCTs that were published in the last 10 years will be screened.

Experts in the field, involved in International vitamin D guidelines, Professors Paul Lips, Michael Holick and Roger Bouillon, will be contacted to enquire about any trial that could be relevant to our review and that would not have been caught by our search.

## **III-Study selection:**

References retrieved in the search strategies will be reviewed in duplicate and independently by reviewers. One reviewer (MC) will screen all references. Two other reviewers (SG and KS) will partake references screening and each one of them will screen half of the references. After exclusion of duplicates (duplicates retrieved from different databases (using endnote library) and duplicate reporting using manual check), screening of abstracts will be done based on our PICO question. We will retrieve the full text of citations included by at least one reviewer. Full texts of retrieved articles will be screened in duplicate and independent manner, using a standardized screening form. A calibration exercise will be done on a sample of abstracts and full texts to make sure screening by reviewers abides by the standardized forms. Disagreements will be resolved by discussion with an expert author (GEHF).

## **IV-Data collection process:**

We will develop a priori a data collection form. It will be pilot tested on 4 randomly included articles and refined accordingly. Data extraction will be done in duplicate and independently. One review author (MC) will extract relevant data from all included studies. Two other review authors (SG and KS), independently, will partake data extraction of included studies whereby every one of them will extract data from half of the included studies. Disagreement between reviewers will be resolved by discussion; if disagreement will not be reached, an expert author (GEHF) will intervene to make a decision.

In case of missing data, authors will be contacted by email. In case of Non-English articles, translation into English will be implemented.

Figure 1. shows the flow diagram of the systematic review.

## **V-Data items:**

Information will be extracted from each trial on the following characteristics:

-Characteristics of study participants, per each treatment arm:

- Country of origin.
- Age.
- Sex.
- Ethnicity.
- Presence or absence of comorbidities.
- Presence or absence of medications.
- Mean BMI.
- Mean 25(OH)D level at baseline
  - Vitamin D assay used (RIA, ELISA, LCMS, HPLC, etc..)
  - Laboratory quality assurance: DEQAS...

-Characteristics of intervention:

- Type of vitamin D supplemented (D2 or D3).
- Vitamin D vehicle.
- Dose.
- Frequency.
- Duration.
- Compliance.
- Presence or absence of concomitant calcium administration.
- Comparator used
  - Placebo
  - Vitamin D: Type, Dose, frequency, vehicle, presence or absence of concomitant calcium supplementation.

-Characteristics of outcome measure, per each treatment arm:

- Proportion of individuals who reach 25(OH)D  $\geq$  20 ng/ml and mean 25(OH)D level at the end of the study.
- Mean serum calcium, PTH, fasting blood glucose, HbA1c, HDL, LDL, TG levels and mean urinary calcium level.
- Muscle strength and other muscle parameters (handgrip strength, jump height ... ).
- Incidence of hip fracture.
- Incidence of hypercalcemia.
- Incidence of kidney stones.
- Incidence of fall and imbalance episodes.
- Mortality.
- Other adverse events.

#### **VI-Risk of bias in individual studies:**

The risk of bias of each individual study will be assessed by two reviewers in duplicate and independently, using the Cochrane Collaboration's tool (Cochrane Handbook 2011). The risk of bias will



be assessed at the level of seven domains: adequacy of randomization, concealment of allocation, blinding of participants and personnel, blinding of outcome assessors, extent of loss to follow-up (incomplete outcome data), selective outcome reporting and other sources of bias. For each domain, judgment will be done qualitatively, answered as yes/no/unclear, based on answering a specific question, and as described in the Cochrane Handbook. An answer “yes” indicates a low risk of bias. An answer “No” indicates a high risk of bias. “Unclear” judgment is made when the risk of bias is unknown. A calibration exercise will be done to ensure adequate assessment by different reviewers.

#### **VII-Summary measures:**

Continuous outcomes will be expressed as mean differences (MD) with 95% confidence interval (CI).

Dichotomous outcomes will be expressed as risk ratio (RR) and hazard ratio (HR) with 95% CI.

Our primary outcome is the mean difference in 25(OH)D level reached between any two treatment arms (placebo versus high dose, placebo versus low dose, placebo versus moderate dose, low dose versus high dose, low dose versus moderate dose and moderate dose versus high dose), and in each age category (infants 0-1 year, children and adolescents 1-18 years, adults 18-65 years, elderly > 65 years) and in pregnant women.

We will determine also the proportion of individuals who reach a 25(OH)D level  $\geq 20$  ng/ml and the mean 25(OH)D level reached by 97.5% of individuals in different treatment groups.

We will calculate the RR and 95% confidence interval (CI) of hip fracture, kidney stones, hypercalcemia/hypercalciuria, falls and imbalance episodes, mortality and other adverse events in vitamin D groups compared to placebo, or in different vitamin D groups. We will calculate the mean difference in serum calcium and PTH, fasting blood glucose, HbA1c, HDL, LDL, and TG level, urinary calcium level, muscle strength and BMD in vitamin D groups compared to placebo groups or in different vitamin D groups. For mortality, if available information, hazard ratio (HR) and 95% CI will be calculated. Quantitative analysis will be done on an intention to treat analysis.

#### **IX-Planned methods of analysis:**

A meta-analysis will be done when at least 2 studies are available for each comparison, in each age category. If at least 10 studies will be retrieved for each age category, a meta-regression will be used to assess the effect of vitamin D supplementation dose, in addition to other covariates (type of vitamin D (D2 vs D3), duration of the intervention, gender, baseline 25(OH)D level, BMI) on serum 25(OH)D level. The primary analysis will be done using a random-effects model. To test the robustness of our results, a fixed effect model will be used also.

Assessment of heterogeneity:

Statistical heterogeneity between studies will be assessed using Chi square with significance at p-value  $\leq 0.1$ . The quantitative assessment of heterogeneity will be done using  $I^2$ .

In case of heterogeneity, pre-specified sub-group analysis will be done.

**X-Risk of bias across studies:**

The risk of bias will be assessed for the included studies:

-Publication bias will be assessed by doing a funnel plot of included studies. For each trial, we will plot the effect by the inverse of its standard error..

The symmetry of the funnel plot will be checked visually and formally with Egger's test.

-Selective outcome reporting will be assessed by looking for the availability of a published protocol for each included study. Otherwise, the methods will be explored and the reported pre-planned outcomes will be compared with the outcomes cited in the results. The Cochrane Collaboration's tool (Cochrane Handbook 2011) for bias assessment will be used to make our judgment.

**XI-Additional analysis:**

Subgroup analyses are pre-specified.

In case of heterogeneity in results, subgroup analysis will be done, based on covariates that we expect them to affect the response to vitamin D supplementation and 25(OH)D level, as follows:

- Vitamin D assays, well known to affect 25(OH)D level (31, 32).
- Type of vitamin D, D2 vs D3, since D2 may raise 25(OH)D to a lesser extent compared to D3 (5).
- Presence or absence of concomitant calcium supplementation, as side effects secondary to calcium might reduce compliance, as well as a direct effect on 25(OH)D level, reflecting decreased 25(OH)D metabolism (33, 34).
- Gender, universal confounder (18, 19).
- Obesity as BMI might be one of the predictors of circulating 25(OH)D level (34).

Sensitivity analysis will be performed in order to assess the effect of relevant factors on the effect measure, if applicable, as follows:

- restricting the analysis to published trials only.
- restricting the analysis to MENA individuals living in MENA countries exclusively
- restricting the analysis to studies with baseline 25(OH)D < 50 nmol/L, since lower baseline vitamin D levels respond more to vitamin D supplementation (20, 35)

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Figure 1: Flow diagram of different steps of the systematic review:

Identification:

Number of records identified from database search: Medline, Embase, Pubmed, Cochrane Library

Number of records identified from Middle East Database: Popline, Global Health and Index Medicus, and trial registries, clinicaltrial.gov and ICTRP

Screening:

Number of records after duplicate removal

Number of records\* screened

Number of records excluded

Eligibility:

Number of full text articles assessed for eligibility

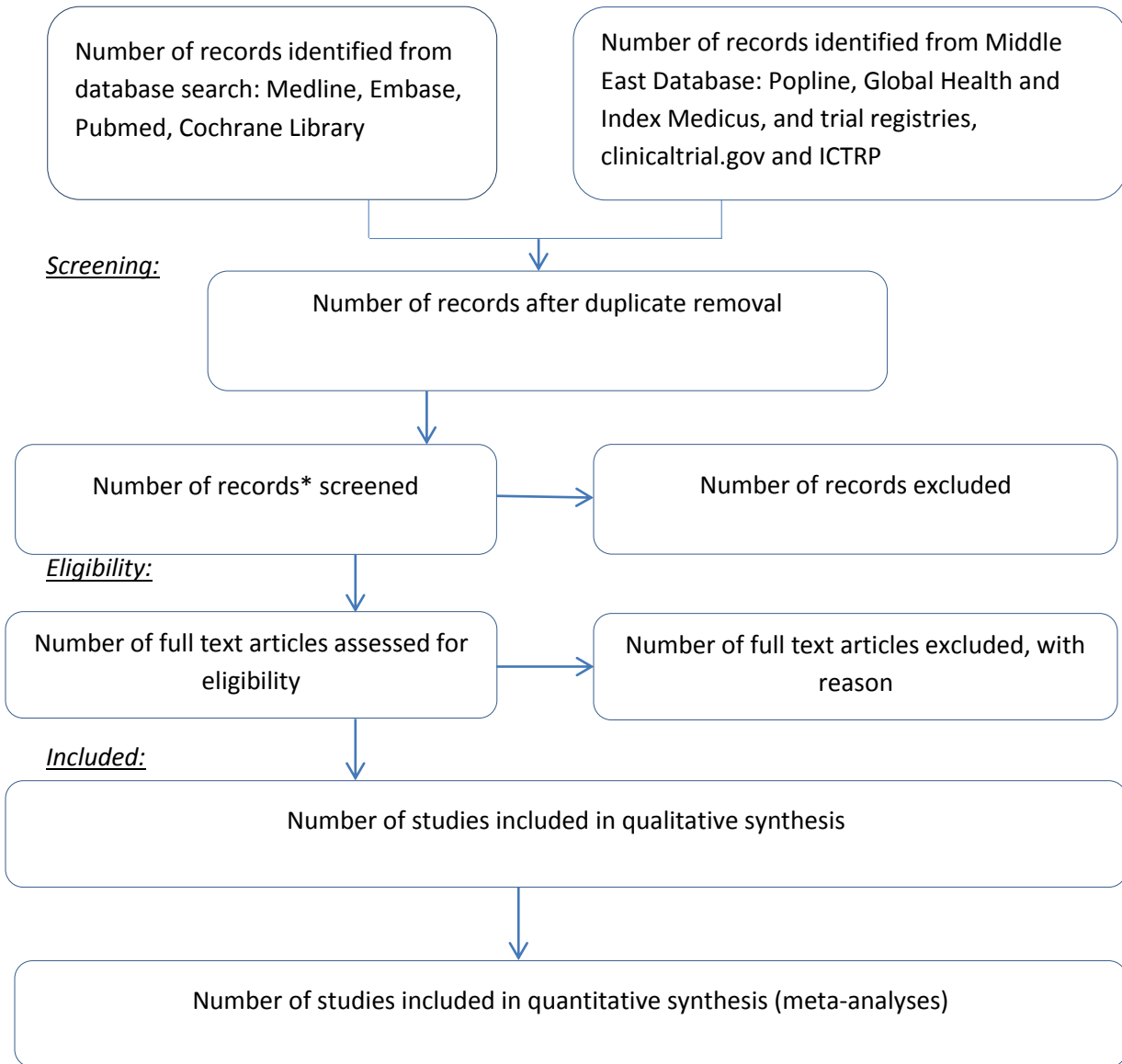
Number of full text articles excluded, with reason

Included:

Number of studies included in qualitative synthesis

Number of studies included in quantitative synthesis (meta-analyses)

\*Titles and abstracts



## Appendix 1:

### A-Rationale for target vitamin D level considered by Endocrine society (2011)

Target 25(OH)D level	Reason	Studies Author /Journal / year	Country/Population N Gender Age	Study design Outcomes
30 ng/ml	1-PTH levels are inversely associated with 25(OH)D level, PTH level reaches a plateau when 25(OH)D level is between 30-40 ng/ml.	Thomas et al NEJM 1998	Boston (inpatient) N=290 Men and women, 18-95 years	Cross sectional Prevalence and risk factors for vitamin D deficiency
		Chapuy et al JCEM 1996	France (general community) N=440 Women, 75-90 years	Cohort Incidence of senile secondary hyperparathyroidism
		Holick et al JCEM 2005	North America (community-dwelling) N=1536 Women, >55 years	Cohort 25(OH)D level and risk factors for vitamin D deficiency
	2-When 25(OH)D level increases from 20 to 32 ng/ml in post-menopausal women, calcium absorption increases from 45-65%.	Heany et al J Am Coll Nut 2003	Omaha N=24 per arm Post-menopausal women	Experimental Quantify calcium absorption at two levels of vitamin D repletion
	3-25(OH)D level $\geq$ 30 ng/ml is required for hip and non-vertebral fracture prevention, result from a meta-analysis of RCT	Bischoff Ferrari et al, Arch Int Med 2005, 2009 and OI 2010	Community dwelling and institutional	Meta-analysis of RCT: Dose response effect on fall and hip/non vertebral fracture prevention
	4-No pathologic osteoid accumulation at 25(OH)D level >30 ng/ml	Priemel et al JBMR 2009	Germany N=675 Men and women, 40-80 years	Cohort The minimum required 25(OH)D level to prevent pathologic osteoid accumulation, based on iliac biopsy

## B-Rationale for target vitamin D level considered by IOM (2010)

Target 25(OH)D level	Reason	Studies Author /Journal / year	Country/Population N Gender Age	Study design Outcomes
20 ng/ml	1-PTH data	Review of the literature does not show widespread agreement on a plateau of serum PTH level consistent with a serum 25OHD level of 75 nmol/l. In most cases, serum PTH level reaches a plateau at different levels of serum 25OHD varying between 37.5 and 125.0 nmol/L		
	2- Calcium absorption remains stable across a range of 25(OH)D levels 30-150 nmol/l	Abrahams et al J Pharmacol Exp Ther. 2009	Children N=251 4.9-16.7 years	Cross sectional Change in calcium absorption according to 25(OH)D level
		Need et al JBMR 2008	US N=319 Men, 56-76 years	Cross sectional Change in calcium absorption according to 25(OH)D level
		Kinyamu et al Am J Clin Nut 1998	US N=376 Post-menopausal women	Cross sectional 25(OH)D level and calcium absorption
		Hansen et al 2008	Wisconsin N=73 Post-menopausal women, 51-67 years	Cohort 25(OH)D level and calcium absorption
		Zhu et al JBMR 2008	Australia N=150 /arm Post-menopausal women, 70-90 years	RCT Calcium absorption according to vitamin D supplementation (1000IU vs placebo)
		Aloia et al Am J Clin Nut 2010	US N=492 Men and women, 20-80 years	25(OH)D and 1,25(OH) <sub>2</sub> D levels prediction of the change in calcium absorption
	3-25(OH)D level ≥ 20 ng/ml prevented osteomalacia in ≥97.5% of the population	Priemel et al* JBMR 2009	Germany N=675 Men and women, 40-80 years	Cohort The minimum required 25(OH)D level to prevent pathologic osteoid accumulation, based on iliac biopsy
	4-Fracture risk RCT presented very variable levels; observational studies were considered.	Ensrud et al JCEM 2009	US (MrOs) N=1279 Men, >65 years	Cohort 25(OH)D levels are and rates of hip bone loss
		Cauley et al JBMR 2011	US (WHI) N=2,246 Post-menopausal women	Nested case control 25(OH)D level and fracture risk

\* Same study cited in the Endo society guidelines, although the authors' conclusion was that a 25(OH)D level of 30ng/ml is required to guarantee bone health.

**Appendix 2: Studies cited in the IOM and Endocrine Society guidelines, to define recommended vitamin D dose in each age category**

Age category	IOM	Endocrine society
0-1 year	<p>400 IU</p> <p><i>Aim is to get optimal D level.</i></p> <p><b>No RDA but AI:</b> Intake of vitamin D 400 IU/day appears to maintain a serum 25OHD level generally above 50 nmol/L in infants.</p> <p>Ala-Houhala et al (1985), Finland RCT Placebo versus vitamin D 400IU daily versus vitamin D 1000IU daily → no rickets in vitamin D groups</p> <p>Greer et al (1989), Wisconsin RCT Placebo versus vitamin D 400IU daily → supplemented group only reached 25(OH)D level ≥ 21 ng/ml</p>	<p>400-1000 IU</p> <p>Feliciano et al (1994), China RCT Vitamin D 100 versus vitamin D 200 versus vitamin D 400IU daily → No effect on weight and height at 6 months</p> <p>Formon et al (1966), Iowa RCT Vitamin D 350-550 versus vitamin D 1,380- 2,170IU daily → no difference in growth rate</p> <p>Specker et al (1992), China RCT Vitamin D 100 versus vitamin D 200 versus vitamin D 400 IU daily. → Increased 25(OH)D level with increasing dose, none had rickets and supplementation with vitamin D 400IU is prudent.</p> <p>Markestad and Elzouki (1991), Norway Review article → vitamin D 300IU daily is required to get 25(OH)D of 11 ng/ml</p> <p>Hyponen et al (2001), Finland Observational Vitamin D 2000 IU daily decreased the incidence of DM type 1 by 88%</p>
1-18 years	<p>600IU</p> <p><i>Aim is to ensure normal, healthy bone accretion is central to the DRI values.</i></p> <p>Ala-Houhala et al(1988), Finland RCT Vitamin D 400IU daily versus Placebo → 25(OH)D level increased from 46 nmol/l to 71 nmol/l in D group.</p> <p>Schou et al(2003), Denmark RCT Vitamin D 600IU daily versus placebo → 25(OH)D level reached 50 nmol/l in D group only</p> <p>Viljakainen et al(2006), Finland RCT Placebo versus vitamin D 200IU versus vitamin D 400IU daily → 25(OH)D level reached 42 vs 51 vs 58.8 nmol/l.</p>	<p>600-1000 IU</p> <p>Urashima et al (2010), Japan RCT Vitamin D 1200IU daily versus placebo → 1200 IU daily decreased the incidence of influenza A by 42%</p> <p>Dong et al (2010), Richmond (African American) RCT Vitamin D 200 IU versus vitamin D 400 IU daily → Higher D levels and lower arterial stiffness</p> <p>Aksnes et al (1982), abstract only Observational Dietary vitamin D 100-400 IU to maintain 25(OH)D above 11 ng/ml</p> <p>Gultekin et al (1987), Turkey Observational → Vitamin D intake &lt;100 IU daily leads to 25(OH)D level &lt;11</p>



Age category	IOM	Endocrine society
	<p>Rajakumar et al(2008), Pittsburgh Observational, all received vitamin D 400IU daily and compared obese versus non obese</p>	<p>ng/ml</p> <p>Maalouf et al (2008), Lebanon RCT in boys Placebo versus vitamin D3 1400 IU versus vitamin D3 14000 IU weekly →25(OH)D level increased from 15 to 19 ng/ml in low dose group and from 15 to 36 ng/ml in high dose group; no toxicity</p> <p>El hajj Fuleihan et al (2006), Lebanon RCT in girls Vitamin D3 1400 IU weekly versus vitamin D3 14000 IU weekly →25(OH)D level increased from 14 to 17 ng/ml in low dose group and from 14 to 38 ng/ml in high dose group; no toxicity</p>
19-50 years	600 IU	1500-2000IU
	<p><i>Aim is bone maintenance.</i></p> <p>Cashman et al(2009), Ireland RCT Placebo versus vitamin D 200 versus vitamin D 400 versus vitamin D 600 IU daily →25(OH)D level &gt;25 nmol/l in ≥ 97% of the population requires 7.9-42.8 mcg daily depending on sun exposure</p> <p>Smith et al (2009), Antarctica vitamin D 400 versus vitamin D 1000 versus vitamin D 2000 IU daily →25(OH)D level increased from 45 nmol/l to 55, 63 and 71 nmol/l</p> <p>Valjakainen et al(2009),Finland RCT Placebo vs vitamin D 400 versus vitamin D 700IU daily →baseline 60 nmo/l→drop in placebo,75 nmol/l , 90 nmol/l</p> <p>Biancuzzo et al(2010), Boston RCT Placebo versus vitamin D2 1000IU versus vitamin D3 1000 daily→25(OH)D levels reached 45, 70, 58 nmol/l</p>	<p>Bischoff Ferrari et al (2004), NHANES Observational Highest quintile(25(OH)D&gt;39 ng/ml in white and &gt;31 ng/ml in African American) had a higher mean BMD</p> <p>Holick et al (2008), Boston RCT Placebo versus vitamin D2 1000 IU daily versus vitamin D3 1000IU daily versus vitamin D2 500IU + D3 500IU daily →in vitamin D groups, 25(OH)D level increased from 19-30 ng/ml (in the deficient group ,none reached a level &gt; 30 ng/ml)</p> <p>Pietras et al (2010),US Retrospective Vitamin D 50000 IU every other week for 6 years →Mean 25(OH)D level reached was 46 ng/ml →No toxicity</p>

Age category	IOM	Endocrine society
	<p>Harris (2002), Boston RCT Placebo versus vitamin D 800 25(OH)D levels reached 48 to 53 vs 59 to 82 nmol/l</p> <p>Heany et al(2003), Omaha RCT Placebo vs D 1000 vs 5000 vs 10000IU daily → 25(OH)D levels reached 52, 77,150 ,212 nmol/l</p> <p>Holick et al (2008), Boston RCT Placebo versus vitamin D2 1000 IU versus vitamin D3 1000IU versus vitamin D2 500IU + D3 500IU → in D groups, 25(OH)D level increased from 19-30 ng/ml (in the deficient group ,none reached a level &gt; 30 ng/ml)</p> <p>Li-Ng et al (2009), Long Island RCT Placebo versus vitamin D 2000 IU daily → Baseline mean 25(OH)D &gt;60 nmol/l, reached mean 25(OH)D level 88 nmol/l in D group</p> <p>Nelson et al(2009), Bangor RCT Placebo versus vitamin D 800 → baseline mean 25(OH)D &gt;60 nmol/l and reached mean 25(OH)D level 97nmol/l in the vitamin D group</p>	
50-70 years	600IU	1500-2000IU
>70 years	800IU	1500-2000IU
	<p>50-70 years: <i>Aim is to reduce peri-menopausal bone loss</i> &gt;70 years: <i>Aim is to reduce fracture risk</i></p> <p>Cashman et al (2009),Ireland RCT Placebo versus vitamin D 200 versus vitamin 400 versus vitamin D 600 IU daily → baseline 25(OH)D level &gt;50 nmol/l Levels reached are 41, 53, 69 and 73 nmol/l, respectively in treatment arms.</p>	<p><u>Bone health and fractures:</u></p> <p>Greene Finestone (2011), Canada RCT Placebo vs D 400IU daily → Vitamin D &gt; 400IU daily is needed to keep 25(OH)D&gt; 50 nmol/l</p> <p>Dawson-Hughes et al (1991), US RCT Placebo versus vitamin D 400IU daily → Increasing vitamin D intake by 400IU is needed to increase bone density in post-menopausal women</p>

Age category	IOM	Endocrine society
	<p>Honkanen et al (1990), Finland RCT Placebo versus vitamin D 1800 IU daily → 25(OH)D level increased from 40 to 80 nmol/l in D group</p> <p>Van Der Kils et al (1996), Netherlands RCT Placebo versus vitamin D 400 versus vitamin 800 IU daily. → 25(OH)D level increased similarly in vitamin D 400 and 800 groups from 60 to 87.9 nmol/l</p> <p>Dawson Hughes et al (1991), Boston RCT Placebo versus vitamin D 400IU daily → increasing D intake by 400IU daily improves bone density in post-menopausal women</p> <p>Harris et al (2002), Boston RCT Placebo versus vitamin D 800IU daily → vitamin D group increased from 61 to 83 nmol/l</p>	<p>Lips et al (1988), US RCT: placebo versus vitamin D 400IU daily → Vitamin 400 IU is needed to increase 1,25D level and decrease PTH</p> <p>Chapuy et al (1992), France RCT Placebo vs D 800IU daily → 800 IU decreases hip and non-vertebral fractures</p> <p>Dawson Hughes (1997), US RCT Placebo versus vitamin D 700IU daily → Vitamin D decreases bone loss and reduces non vertebral fracture</p> <p>Bischoff Ferrari 2005 and 2009 Meta-analysis Vitamin D700-800IU daily is required to reach 25(OH)D level ≥ 30 ng/ml Vitamin D 480-770IU daily is required to decrease non vertebral fractures</p> <p><u>Muscle:</u></p> <p>Pfeifer et al (2000), Germany Ca + vitamin D 800IU daily versus Calcium only D 800IU daily improves body sway and decreases falls</p> <p>Murad et al (2011), Meta-analysis Vitamin D supplementation is associated with fall reduction (OR 0.79); dose response was not assessed and high heterogeneity.</p> <p>Pfeifer et al (2009), Austria and Germany RCT Calcium vs Calcium + vitamin D 400IU daily → Vitamin D 400IU daily decreases falls</p> <p>Broe et al (2007), US RCT Vitamin D 200 versus vitamin D 400 versus vitamin D 600 versus vitamin D 800 IU daily → Vitamin D 800IU daily decreases fall by 72 %</p>

Age category	IOM	Endocrine society
		Graafmans et al (1996), Netherlands RCT Vitamin D 400IU vs placebo ➔ Vitamin D was not related to falls or recurrent falls

## Appendix 3: Search Strategy

### Medline search:

1. exp Vitamin D/
2. Vitamin D Deficiency/
3. ((avitamin\* or hypovitamin\* Hypervitamin\* or plivit or glycol or davitamon or chemovit or arthrin\* or crivit or vita\* or vitasan or vio or idro\* or inovitan or vitastab\* or vatin\* or difvitamin or uvesterol or wandervit or vitavel or oleovit or oleovitamin or min\* or vitamin\* or hydroxyvitamin\* or (hydroxy adj vitamin\*) or dihydroxyvitamin\* or (dihydroxy adj vitamin\*)) adj3 (d or d2 or d3)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. (vitamind\* or cholecalciferol\* or calciol\* or calcitriol\* or hydroxycholecalciferol\* or (hydroxy adj cholecalciferol\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. (dihydroxycholecalciferol\* or (dihydroxy adj cholecalciferol\*) or ergocalciferol\* or calcifediol\* or calcidol\* or calderol\* or dedrogyl\* or calciferol\* or hidroferol\* or calcijex or sitriol\* or silkis or osteotriol\* or soltriol\* or decostriol\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. (renatriol\* or rocaltrol\* or tirocal\* or dihydrotachysterol\* or (dihydro adj tachysterol\*) or tachystin\* or calcamin\* or dihydrotachysterin\* or (dihydro adj tachysterin\*) or ercalcidiol\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. (bocatriol\* or alphacalcidiol\* or (alpha adj calcidiol\*) or alfalcacidiol\* or (alfa adj calcidiol\*) or colecalciferol\* or ercalcitriol\* or sterogyl\* or (euro adj d) or hydroxyergocalciferol\* or (hydroxy adj ergocalciferol\*) or hydroxycalciferol\* or (hydroxy adj calciferol\*) or calcitriolnefro\* or (calcitriol adj nefro\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. (secoergosta or secocholesta or Diol\* or delakmin\* or didrogyl or dydrogil or alcovit\* or aldevit\* or bentavit or calciferovit\* or drisdol or ergosterol\* or devaron or duphafraal or dupharinterfran or irradiia or irradiian or ostoforte or uvedose\* or vigantol or vigorsan or viosterol\* or arachitol or calciol or condol or davitan or davitin or sterogyl\*OR vitaplex or osteovit\* or sterosol or ercalcilol or didrol or desyn\* or diferol\* or drisdol\* or ergosteri\* or fortifiedol or fortodyl\* or sterodin\* or ostelin or vitasterol or feroxyl\* or shockferol\* or infron\* or vitadit or vid\*OR sterobiol or kalciferol\* or raquiferol\* or sterovit or vioster\*OR vitaminol or vitasterin or mukostin or radiamon or radiostol or radsterin\* or radsterin\* or delta\* or derad\* or diergin\* or calciosterina or osteod\*OR osteovit\* or ertron\* or steramin\* or vitasterin\* or mulsiferol\* or oldevit or dergosten or deeosterol or deratol or detalup or deterap\* or devit\* or diactol or disterin\* or ostergil or ergorone or feroxyl\* or ostelin\*OR infad\* or steral or dekristol or activatum or diviturto or idrosol).ti,ab.
9. or/1-8
10. exp Middle East/
11. exp Africa, Northern/ or exp Djibouti/

12. (gaza or (west\* adj2 bank)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. ((Middle adj2 east\*) or mid-east\* or (mid adj east\*) or arab\* or orient\* or (near adj2 east\*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. (MENA or leban\* or syri\* or yemen\* or Iraq\* or irak\* or KSA or UAE or saudi\* or Kuwait\* or gulf\* or bahrain\* or transjordan\* or jordan\* or qatar\* or quatar\* or katar\* or Israel\* or palestin\* or djibout\* or persia\* or iran\* or malt\* or oman\* or byzanti\* or fertile crescent or (islamic adj republic\*) or (united adj arab\* adj (emirat\* or republic))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15. (beirut\* or beyrouth or damascus or sana\* or baghdad or riyadh\* or dubai or (trucial adj stat\*) or (abu adj dhabi) or manama or amman or doha or ghaza or (tel adj aviv) or haifa or jerusalem or ramallah or tehran or muscat or valetta).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. ((north\* adj2 africa\*) or (french adj speaking adj africa\*) or aden or maghrib\* or maghreb\* or sahara or algeri\* or alger\* or egypt\* or mediterranean\* or cairo or liby\* or libi\* or tripoli or morocc\* or rabat or tunisi\* or tunesi\* or ifni).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17. or/10-16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized.ab.
21. placebo.ab.
22. placebo.ab.
23. clinical trials as topic.sh.
24. randomly.ab.
25. trial.ti.
26. or/18-25
27. exp animals/ not humans.sh.
28. 26 not 27
29. 9 and 17 and 28

### PubMed Search:

((((((((((((((((((randomized controlled trial[pt]) OR controlled clinical trial[pt]) OR randomized[tiab]) OR drug therapy[sh]) OR randomly[tiab]) OR trial[tiab]) OR groups[tiab]) OR placebo[tiab]) NOT (animals[mh] NOT humans[mh]))))))) AND (((((((((((((((middle east) OR middle east) OR north africa) OR djibouti) OR (middle east\* OR mid-east\* OR mid east\* OR arab OR arabian OR arabic OR orient\* OR near east\*)) OR ((MENA OR leban\* OR syri\* OR yemen\* OR Iraq\* OR irak\* OR KSA))) OR ((UAE OR saudi\* OR Kuwait\* OR gulf\* OR bahrain\* OR transjordan\* OR jordan\* OR qatar\* OR quatar\* OR katar\* OR Israel\* OR palestin\* OR djibout\* OR persia\* OR iran\* OR malta OR oman\* OR byzanti\*)) OR (united arab\* AND emirat\*)) OR united arab\* AND republic\*) OR gaza) OR (((west OR western) AND bank))) OR ((beirut\* OR beyrouth OR damascus OR sanaa OR baghdad OR riyadh\* OR dubai OR abu dhabi OR manama OR amman OR doha OR ghaza))) OR ((tel aviv OR haifa OR jerusalem OR ramallah OR tehran OR

muscat OR aden OR maghrib\* OR maghreb\* OR sahar\* OR algeri\* OR algier\* OR egypt\* OR mediterranean\* OR cairo OR liby\* OR libi\* OR tripoli OR morocc\* OR rabat OR tunisi\* OR tunesi\* OR ifni\*)) OR (((north\* OR french) AND africa\*)))) AND (((((((((((vitamin d) OR cholecalciferol) OR vitamin d deficiency) OR ((vitamind\* OR cholecalciferol\* OR calciol\* OR calcitriol\* OR hydroxycholecalciferol\* OR (hydroxy cholecalciferol\*)))) OR ((avitamin\* OR vitamin\* OR Hypervitamin\* OR glycol OR davaamon OR arthrin\* OR vita OR vio OR idro\* OR uvesterol OR oleovit OR oleovitamin OR mina OR hypovitamin\* OR hydroxyvitamin\* OR (hydroxy vitamin\*) OR dihydroxyvitamin\* OR (dihydroxy vitamin\*)) AND (d OR d2 OR d3))) OR ((dihydroxycholecalciferol\* OR (dihydroxy cholecalciferol\*) OR ergocalciferol\* OR calcifediol\* OR calcidiol\* OR calderol\* OR dedrogyl\* OR calciferol\* OR hidroferol\* OR calcijex OR soltrioi\* OR rocaltrol\* OR tirocal\* OR dihydrotachysterol\* OR (dihydro tachysterol\*) OR tachystin\* OR calcamin\* OR dihydrotachysterin\* OR ercialcidiol\*)) OR ((alphacalcidiol\* OR (alpha calcidiol\*) OR alfacalcidiol\* OR (alfa calcidiol\*) OR colecalciferol\* OR ercialcitril\* OR sterogyl\* OR (euro d) OR hydroxyergocalciferol\* OR (hydroxy ergocalciferol\*) OR hydroxycalciferol\* OR (hydroxy calciferol\*)))) OR ((secoergosta[tiab] OR secocholesta[tiab])))

### Embase Search:

#1.30

#1.13 AND #1.23 AND #1.29

#1.29

#1.24 OR #1.25 OR #1.26 OR #1.27 OR #1.28

#1.28

random\* OR factorial\* OR crossover\* OR cross NEAR/2 over\* OR placebo\* OR doubl\* NEAR/2 blind\* OR singl\* NEAR/2 blind\* OR assign\* OR allocat\* OR volunteer\*

#1.27

'single blind procedure'/exp

#1.26

'randomized controlled trial (topic)'/exp

#1.25

'double blind procedure'/exp

#1.24

'crossover procedure'/exp

#1.23

#1.14 OR #1.15 OR #1.16 OR #1.17 OR #1.18 OR #1.19 OR #1.20 OR #1.21 OR #1.22

#1.22

north\* NEAR/2 africa\* OR (french AND speaking AND africa\*) OR aden OR maghrib\* OR maghreb\* OR sahara OR algeri\* OR algier\* OR egypt\* OR mediterranean\* OR cairo OR liby\* OR tripoli OR morocc\* OR rabat OR tunisi\* OR tunesi\* OR libi\* OR ifni

#1.21

beirut\* OR beyrouth OR damascus OR sana\* OR baghdad OR riyadh\* OR trucial NEAR/2 stat\* OR abu NEAR/2 dhabi OR manama OR amman OR doha OR ghaza OR tel NEAR/2 aviv OR haifa OR jerusalem OR ramallah OR tehran OR muscat OR valetta OR dubai OR byzanti\* OR transjordan\* OR persia\* OR islamic NEAR/2 republic\* OR fertile NEAR/2 crescent

#1.20

united AND arab\* NEAR/2 (emirat\* OR republic\*)

#1.19

middle NEAR/2 east\* OR mid NEAR/2 east\* OR arab\* OR orient\* OR near NEAR/2 east\*

#1.18

'malta'/exp

#1.17

'yemen'/exp

#1.16

'djibouti'/exp

#1.15

'north africa'/exp

#1.14

'middle east'/exp

#1.13

#1.1 OR #1.2 OR #1.3 OR #1.4 OR #1.5 OR #1.6 OR #1.7 OR #1.8 OR #1.9 OR #1.10 OR #1.11 OR #1.12

#1.12

secoergosta:ab,ti OR secocholesta:ab,ti

#1.11

bocatriol\* OR alphacalcidiol\* OR alpha NEAR/2 calcidiol\* OR alfacalcidiol\* OR alfa NEAR/2 calcidiol\* OR colecalciferol\* OR ercalcitriol\* OR sterogyl\* OR euro NEAR/2 d OR hydroxyergocalciferol\* OR hydroxy NEAR/2 ergocalciferol\* OR hydroxycalciferol\* OR hydroxy NEAR/2 calciferol\* OR calcitriolnefro\* OR calcitriol NEAR/2 nefro\*

#1.10

dihydroxycholecalciferol\* OR dihydroxy NEAR/2 cholecalciferol\* OR ergocalciferol\* OR calcifediol\* OR calcidiol\* OR calderol\* OR dedrogyl\* OR calciferol\* OR hidroferol\* OR calcijex OR sitriol\* OR silkis OR osteotriol\* OR soltriol\* OR decostriol\*

#1.9

renatriol\* OR rocaltrol\* OR tirocal\* OR dihydrotachysterol\* OR dihydro NEAR/2 tachysterol\* OR tachystin\* OR calcamin\* OR dihydrotachysterin\* OR dihydro NEAR/2 tachysterin\* OR ercalcidiol\*

#1.8

cholecalciferol\* OR diol\* OR delakmin\* OR didrogyl OR dydrogil OR alcovit\* OR aldevit\* OR bentavit OR calciferovit\* OR drisdol OR ergosterol\* OR devaron OR duphafra OR dupharinterfran OR irradiat OR irradiat OR ostoforte OR uvedose\* OR vigantol OR vigorsan OR viosterol\* OR arachitol OR calciol OR condol OR davitan OR davitin OR sterogyl\* OR vitaplex OR sterosol OR ercalciol OR didrol OR desyn\* OR diferol\* OR drisdol\* OR ergosteri\* OR fortedol OR fortodyl\* OR sterodin\* OR ostelin OR vitasterol OR shockferol\* OR infron\* OR vitadit OR vid\* OR sterobiol OR kalciferol\* OR raquiferol\* OR sterovit OR vioster\* OR vitaminol OR vitasterin OR mukostin OR radiamon OR radiostol OR radsterin\* OR delta\* OR derad\* OR diergin\* OR calciosterina OR osteod\* OR osteovit\* OR ertron\* OR steramin\* OR vitasterin\* OR mulsiferol\* OR oldevit OR dergosten OR deeosterol OR deratol OR detalup OR deterap\* OR devit\* OR diactol OR disterin\* OR ostergil OR ergorone OR feroxyl\* OR ostelin\* OR infad\* OR steral OR dekristol OR activatum OR diviturto OR idrosol OR calciol\* OR calcitriol\* OR hydroxycholecalciferol\* OR hydroxy NEAR/2 cholecalciferol\*

#1.7

(dihydroxyvitamin OR avitamin\* OR hypoviatmin\* OR hypervitamin\* OR plivit OR glycol OR davitamon OR chemovit OR arthrin\* OR crivit OR vita\* OR vitasan OR vio OR idro\* OR inovitan OR vitastab\* OR vatin\* OR difvitamin OR uvesterol OR wandervit OR vitavel OR oleovit OR oleovitamin OR min\*) NEAR/2 (d OR d2 OR d3)

#1.6

dihydroxy AND vitamin NEAR/2 (d OR d2 OR d3)



#1.5

hydroxy AND vitamin NEAR/2 (d3 OR d2 OR d)

#1.4

vitamind\* OR (vitamin\* OR hydroxyvitamin\*) NEAR/2 (d3 OR d2 OR d)

#1.3

'vitamin d intoxication'/exp

#1.2

'vitamin d deficiency'/exp

#1.1

'vitamin d'/exp

### Cochrane Library Search:

Search Hits

#1 MeSH descriptor: [Vitamin D] explode all trees

#2 MeSH descriptor: [Vitamin D Deficiency] explode all trees

#3 (avitamin\* or hypovitamin\* or vitamin\* or hydroxyvitamin\* or hydroxy near/2 vitamin\* or dihydroxyvitamin\* or dihydroxy near/2 vitamin\*) near/3 (d or d2 or d3)

#4 vitamind\* or cholecalciferol\* or calciol\* or calcitriol\* or hydroxycholecalciferol\* or hydroxy near/2 cholecalciferol\*

#5 dihydroxycholecalciferol\* or dihydroxy near/2 cholecalciferol\* or ergocalciferol\* or calcifediol\* or calcidol\* or calderol\* or dedrogy\* or calciferol\* or hidroferol\* or calcijex or sitriol\* or silkis or osteotriol\* or soltriol\* or decostriol\*

#6 renatriol\* or rocalcrol\* or tirocal\* or dihydrotachysterol\* or (dihydro near/2 tachysterol\*) or tachystin\* or calcamin\* or dihydrotachysterin\* or (dihydro near/2 tachysterin\*) or ercalcidiol\*

#7 bocatriol\* or alphacalcidiol\* or alpha near/2 calcidol\* or alfacalcidiol\* or alfa near/2 calcidol\* or colecalciferol\* or ercalcitriol\* or sterogyl\* or euro near/2 d or hydroxyergocalciferol\* or hydroxy near/2 ergocalciferol\* or hydroxycalciferol\* or hydroxy near/2 calciferol\* or calcitriolnefro\* or calcitriol near/2 nefro\*

#8 secoergosta or secocholesta 0

#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

#10 MeSH descriptor: [Middle East] explode all trees

#11 MeSH descriptor: [Africa, Northern] explode all trees

#12 MeSH descriptor: [Djibouti] explode all trees

#13 gaza or (west\* near/2 bank)

#14 Middle near/2 east\* or mid east\*

#15 mid near/2 east\* or arab\*

#16 orient\* or east\*

#17 MENA or leban\* or syri\* or yemen\* or Iraq\* or irak\* or KSA or UAE or saudi\* or Kuwait\* or gulf\* or bahrain\* or transjordan\* or jordan\* or qatar\* or quatar\* or katar\* or Israel\* or palestine\* or djibout\* or persia\* or iran\* or malt\* or oman\* or byzanti\* or fertile crescent

#18 islamic near/2 republic\* or (united near/2 arab\* near/2 (emirat\* or republic))

#19 beirut\* or beyrouth or damascus or sana\* or baghdad or riyadh\* or dubai or (trucial near/2 stat\*) or (abu near/2 dhabi) or manama or amman or doha or ghaza or (tel near/2 aviv) or haifa or jerusalem or ramallah or tehran or muscat or valetta

#20 (north\* near/2 africa\*) or (french near/2 speaking near/2 africa\*) or aden or maghrib\* or maghreb\* or sahara or algeri\* or alger\* or egypt\* or mediterranean\* or cairo or liby\* or libi\* or tripoli or morocc\* or rabat or tunisi\* or tunesi\* or ifni

#21 #10 or #11 or #12 or #13 #14 or #15 or #16 or #17 or #18 or #19 or #20

#22 #9 and #21