



# Health Technology Assessment (HTA)

## HTA Scoping Report

Title	Vitamin D Testing
Author/Affiliation	<p>Dr Arjun Bhadhuri, Dr C. Simone Sutherland, Dr Katja Suter-Zimmermann, Prof Dr Matthias Schwenkglens</p> <p>Institute of Pharmaceutical Medicine (ECPM), University of Basel</p> <p>Prof Dr Sabine Rohrmann, Ola Hysaj, Dr Yuki Tomonaga, Giulia Pestoni, Nena Karavasiloglou</p> <p>Epidemiology, Biostatistics and Prevention Institute (EBPI), University of Zürich</p>
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Technology	<p><i>Testing of serum 25-hydroxy-vitamin D concentrations</i></p> <p><i>25-hydroxy-vitamin D (25-OH-D) analysis</i></p>
Type of Technology	<p><i>Laboratory analyses:</i></p> <p><i>Analysenliste Pos.Nr. 1006.00; TP:53;</i></p> <p><i>25-hydroxy-vitamin D (25-OH-D)</i></p>
Keywords	<p><i>Vitamin D; 25-hydroxy vitamin D; 25-OH-D; vitamin D testing</i></p>

## **Executive Summary**

In Switzerland, the utilization of vitamin D tests has increased over 100-fold since 2006, leading to substantial increases in costs. Although vitamin D supplementation is recommended in clinical practice, the benefits of vitamin D testing prior to vitamin D supplementation remain unknown.

We conducted a systematic literature search to identify the clinical and economic evidence related to testing for vitamin D for at-risk groups defined by the Swiss Federal Commission of Nutrition (FCN). We further examined the literature regarding the clinical effect of vitamin D supplementation in the same at-risk groups. If no benefit from supplementation can be shown, then benefits of testing can be ruled out, if these tests aim to inform the decision to supplement.

In regards to vitamin D testing for the defined at-risk groups (persons with bone disorders, older adults, obese individuals, pregnant women, people with dark skin, and athletes), no primary studies were identified which assess health outcomes.

Economic results for testing in older adults were mixed and non-conclusive. In one study, it was estimated that for older people as well as for people with darker skin, overall costs are lower if supplementation of vitamin D without prior vitamin D testing is given instead of implementing a vitamin D testing and treatment strategy.

In regards to vitamin D supplementation, we pursued a systematic but non-comprehensive approach to the literature search and selection, which carries a potential risk of bias. On this basis, the evidence on effectiveness of vitamin D supplementation was generally mixed and not conclusive.

Based on the scoping report the feasibility to produce a full HTA has been considered. A full HTA would not be justified at present due to the absence of clinical studies evaluating vitamin D testing. Only after such studies have become available could the topic be re-considered. Vitamin D testing is recommended for patients where it is medically necessary, and this is not disputed in the present report. The lack of available evidence for vitamin D testing for defined at-risk groups from our review, could be informative in guiding a decision policy on vitamin D testing.

## **Zusammenfassung:**

In der Schweiz hat der Einsatz von Vitamin-D-Tests seit 2006 um mehr als das Hundertfache zugenommen, was zu erheblichen Kostenanstiegen geführt hat. Obwohl eine Vitamin-D-Supplementierung in der klinischen Praxis empfohlen wird, ist der Nutzen von Vitamin-D-Tests vor einer Vitamin-D-Supplementierung nicht bekannt.

Wir führten eine systematische Literaturrecherche durch, um die klinische und wirtschaftliche Evidenz von Vitamin-D-Tests für von der Eidgenössischen Ernährungscommission (EEK) definierte Risikogruppen zu ermitteln. Ferner analysierten wir die Literatur zur klinischen Wirkung einer Vitamin-D-Supplementierung bei denselben Risikogruppen. Wenn kein Nutzen einer Supplementierung nachgewiesen werden kann, lässt sich ein Nutzen der Tests ausschliessen, sofern aufgrund dieser Tests die Entscheidung zur Supplementierung getroffen werden soll.

Hinsichtlich der Vitamin-D-Tests für die definierten Risikogruppen (Personen mit Knochenerkrankungen, ältere Erwachsene, adipöse Personen, Schwangere, Menschen mit dunkler Haut sowie Sportlerinnen und Sportler) wurden keine Primärstudien ermittelt, die den gesundheitlichen Nutzen beurteilen.

Die ökonomischen Ergebnisse des Testens älterer Erwachsener waren gemischt und nicht schlüssig. In einer Studie wurde davon ausgegangen, dass sowohl bei älteren Menschen als auch bei Menschen mit dunkler Haut die Gesamtkosten niedriger sind, wenn eine Vitamin-D-Supplementierung ohne vorherigen Vitamin-D-Test erfolgt und keine Vitamin-D-Test- und -Behandlungsstrategie zur Anwendung gelangt.

In Bezug auf die Vitamin-D-Supplementierung verfolgten wir bei der Literaturrecherche und -auswahl einen systematischen, aber nicht umfassenden Ansatz, der ein potenzielles Risiko für Verzerrung (Bias) birgt. Auf dieser Grundlage war die Evidenz zur Effektivität einer Vitamin-D-Supplementierung im Allgemeinen gemischt und nicht schlüssig.

Aufgrund des Scoping-Berichts wurde die Durchführbarkeit eines vollständigen HTAs erwogen. Ein vollständiges HTA wäre derzeit nicht gerechtfertigt, da es keine klinischen Studien zur Bewertung von Vitamin-D-Tests gibt. Erst nach Vorliegen solcher Studien könnte das Thema neu angegangen

werden. Vitamin-D-Tests werden für Patientinnen und Patienten empfohlen, bei denen sie medizinisch notwendig sind, und dies wird im vorliegenden Bericht nicht bestritten. Der bei unserer Literaturstudie festgestellte Mangel an verfügbarer Evidenz für Vitamin-D-Tests für definierte Risikogruppen könnte aufschlussreich sein, eine Entscheidungsstrategie für Vitamin-D-Tests zu leiten.

### **Résumé:**

En Suisse, les recours aux tests pour mesurer le taux de vitamine D ont été multipliés par plus de 100 depuis 2006, entraînant une hausse considérable des coûts. Bien que l'apport complémentaire en vitamine D soit recommandé en pratique clinique, les avantages de procéder à un test avant la supplémentation elle-même demeurent inconnus.

Nous avons mené une recherche systématique dans la littérature pour identifier les preuves cliniques et économiques relatives au dépistage d'une éventuelle carence en vitamine D dans des groupes à risque définis par la Commission fédérale de la nutrition (CFN). Nous avons également examiné la littérature concernant l'effet clinique de l'apport en vitamine D dans ces mêmes groupes à risque. Au cas où il n'était pas possible de démontrer un bénéfice clinique pour ce qui est de la supplémentation, il serait alors également possible d'exclure un bénéfice clinique pour la mesure du taux de vitamine D pour les cas où celle-ci sert de base à la décision de supplémentation.

Concernant les tests pour la vitamine D dans les groupes à risque définis (personnes atteintes de troubles osseux, personnes âgées, personnes souffrant d'obésité, femmes enceintes, personnes ayant la peau sombre et athlètes), nous n'avons identifié aucune étude primaire évaluant les résultats en matière de santé.

Les résultats économiques pour les tests réalisés au sein de la population âgée étaient mitigés et non concluants. Une étude estimait que, tant pour les personnes âgées que pour les personnes avec une peau sombre, la supplémentation en vitamine D administrée sans test préalable entraînait des coûts totaux moins élevés que si la stratégie mise en place incluait test et traitement.

Pour l'apport supplémentaire en vitamine D, nous avons, lors de notre recherche et de notre sélection, opté pour une approche systématique mais non exhaustive qui comporte un risque de biais. À partir de là, les preuves de l'efficacité de la supplémentation en vitamine D étaient généralement mitigées et non concluantes.

Sur la base du rapport de scoping, la faisabilité de produire un rapport HTA complet a été considérée. Un HTA complet ne serait pour l'instant pas justifié étant donné le manque d'études cliniques consacrées aux tests de dépistage pour la vitamine D. Ce sujet ne pourra être réexaminé qu'une fois que de telles études seront disponibles. Les tests pour la vitamine D sont recommandés aux patients pour lesquels ils s'avèrent médicalement nécessaires, et le présent rapport ne conteste aucunement ce fait. Le manque de preuves disponibles concernant les tests de dosage de la vitamine D pour les groupes à risque définis pourrait constituer une information utile afin d'orienter une politique de décision quant auxdits tests.

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## Abbreviations and Acronyms

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BAG	Bundesamt für Gesundheit (Refer to Swiss FOPH)
CENTRAL	Cochrane Central Register of Controlled Trials
CHEERS	Consolidated Health Economic Reporting Standards
CI	Confidence Interval
CKD	Chronic Kidney Disease
CRD	Centre for Reviews and Dissemination
CRQ	Central research question
EMBASE	Excerpta Medica database
EEACTs	Economic evaluations alongside clinical trials
FCN	Federal Commission of Nutrition
FOPH	Federal Office of Public Health
GBP	Great British Pounds
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIRU	Health Information Research Unit
HTA	Health technology assessment
IBD	Inflammatory bowel disease
ICER	Incremental cost-effectiveness ratio
ICUR	Incremental cost-utility ratio
MA	Meta-analysis
MEDLINE	Medical Literature Analysis and Retrieval System Online
OR	Odds ratio
PICOS	Population, Intervention, Comparator, Outcomes, Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTH	Parathyroid hormone
RCT	Randomized controlled trial
RR	Relative risk
SLR	Systematic Literature Review
SR	Systematic review
UR	Umbrella review
Vitamin D	Vitamin D2 and D3
Vitamin D2	Ergocalciferol
Vitamin D3	Cholecalciferol
25-(OH)D	25-hydroxyvitamin D (=Vitamin D)
1,25-(OH)D	Calcitriol



## **Objective of the HTA Scoping Report**

The objective of the scoping report on vitamin D testing is to conduct a systematic literature search and to synthesize the available evidence base addressing the main health technology assessment (HTA) domains. A central research question is presented and a systematic literature search is conducted to determine whether sufficient evidence is available to conduct a full HTA. The main focus of the literature search is to identify studies evaluating clinical effectiveness and economic impact of vitamin D testing. A second objective is to identify studies evaluating clinical effectiveness of vitamin D supplementation.

Operational key questions covering the EUnetHTA main Core-Model domains, i.e. clinical effectiveness/safety, costs/budget impact/cost-effectiveness, legal/social/ ethical and organisational issues are formulated. The target population(s), the appropriate comparator and the relevant health outcomes are defined. In the report the analytical methods that are to be used when a HTA is pursued are described. Based on quantity and quality of the extracted evidence the feasibility of pursuing a HTA is judged. Analysis of the individual study outcomes is not the objective of the scoping report.

## 1. Policy Question

The Federal Office of Public Health (FOPH) is reviewing the reimbursement by the Swiss compulsory insurance of vitamin D testing compared to no vitamin D testing and/or supplementation of vitamin D without prior vitamin D testing in defined risk groups because the clinical utility of vitamin D testing has been questioned. Currently, vitamin D testing is reimbursed by the Swiss compulsory health insurance for any individual regardless of their level of deficiency risk.

This report from FOPH aims to evaluate the available clinical and economic evidence on vitamin D testing. Over the last 10 years, the amount of prescriptions for vitamin D testing has increased steadily in Switzerland, leading to substantial increases in costs.

In a report by the Federal Commission of Nutrition (FCN), it was recommended that vitamin D testing is undertaken in groups at high risk of severe vitamin D deficiency <sup>1</sup>.

Questions have been raised about the clinical utility of vitamin D testing prior to vitamin D supplementation. Supplementing without vitamin D testing is an alternative treatment pathway recommended in various western countries.

Certain groups at risk may profit from vitamin D testing, as it may inform the decision of a physician of whether to prescribe a vitamin D supplement or not. Also the result of a vitamin D test can inform what the optimal vitamin D dose is for a patient according to his/her level of deficiency. In addition, the question, which groups at risk profit from vitamin D supplementation, is a topic of ongoing debate.

Therefore, simultaneously to addressing vitamin D testing, this scoping report extracts and presents available evidence supporting or not supporting a clinical benefit of vitamin D supplementation in certain groups at risk where FCN recommended vitamin D testing. If no benefit from supplementation can be shown, and if vitamin D tests aim to inform the decision to supplement, then benefits of testing can be ruled out a priori. This perspective becomes particularly relevant in the absence of evidence for testing.

## 2. Research Question

The central research question (CRQ) investigates:

- the clinical utility and economic impact of vitamin D testing in groups at high risk of severe vitamin D deficiency.

### 3. Medical Background

#### ***Vitamin D***

Vitamin D, also known as calciferol, is a liposoluble vitamin obtained either through synthesis in the skin through exposure to ultraviolet B (UVB) radiation from sunlight <sup>2</sup>, or from dietary sources and supplements <sup>3,4</sup>.

Several forms of vitamin D exist, of which vitamin D2 or ergocalciferol and vitamin D3 or cholecalciferol are the most active forms. Vitamin D without a subscript refers to either D2 or D3 or both. Vitamin D2 is derived from plants while vitamin D3 is derived from animal sources and exposure to sunlight which is the main source <sup>5</sup>. Naturally vitamin D rich foods include fatty fish (salmon, tuna, sardines etc.), egg yolks, fish liver oil and certain types of mushrooms <sup>3,6</sup>. Fortified foods (although banned in several countries) such as milk and butter as well as sunlight exposure are more efficient vitamin D sources. Sunlight as source of vitamin D is dependent on age, seasonality, sun exposure, skin pigmentation and sun protective means. It can be difficult to obtain the recommended daily vitamin D intake from natural vitamin D sources only, therefore the use of vitamin D supplements may be necessary in certain subpopulations.

Bone metabolism is characterized by continuous and lifelong bone formation and resorption <sup>7</sup>. Particularly in childhood, bone metabolism is increased and adapted to the needs of skeletal growth <sup>8</sup>. Vitamin D and calcium have a pivotal impact on bone health during pediatric age when nutritional rickets and impaired bone mass acquisition may occur. Besides these classic skeletal actions, recent studies have demonstrated that vitamin D exerts other significant extraskeletal actions.

Vitamin D and calcium deficiencies impair bone density and muscle function at any age, from childhood and adolescence onwards. Additionally negative effects on the immune system, diabetes incidence and cardio-metabolic function have been shown <sup>9</sup>.

#### ***Vitamin D Metabolism and Physiology***

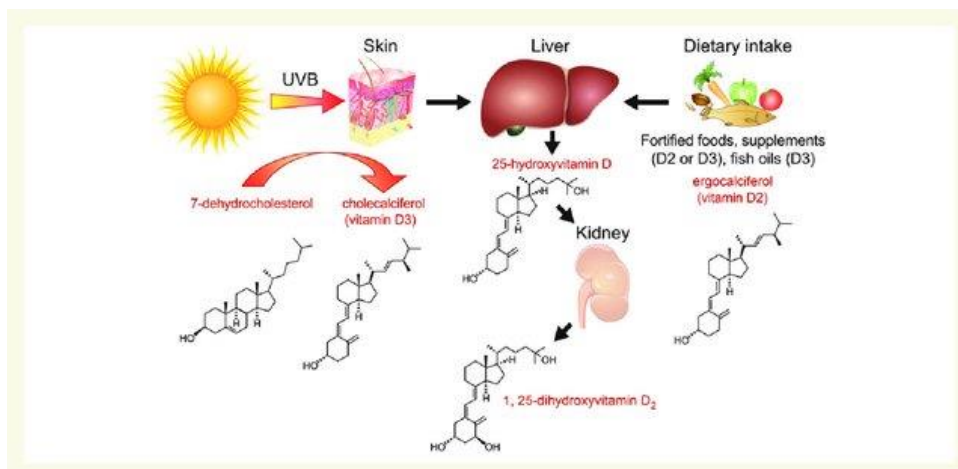
Vitamin D from sunlight exposure, food or supplements first undergoes hydroxylation in the liver producing 25-hydroxyvitamin D. In the kidneys, a second hydroxylation occurs producing 1,25-dihydroxyvitamin D, the active form of vitamin D <sup>5</sup>. This step can also occur in the prostate, colon and breast <sup>10</sup>. Plasma parathyroid hormone (PTH), FGF23, serum calcium and phosphate levels regulate the renal synthesis of 1,25-dihydroxyvitamin D <sup>11</sup>.

The major role of vitamin D is to stimulate intestinal calcium and phosphate absorption. Adequate blood levels of calcium and phosphate are dependent on an adequate level of vitamin D <sup>12,13</sup>. Calcium and

phosphate are important for bone growth, remodelling and mineralization, but also for other physiologic functions, such as muscle functioning<sup>14</sup>. Therefore, calcium deficiency may also be responsible for muscle tetany, besides its negative effect on bone metabolism<sup>15</sup>. The fine regulation of blood levels of calcium and phosphate depends additionally on hormones such as parathormone (PTH) and calcitonin<sup>16 17</sup>.

Vitamin D is also believed to be involved in the regulation of cell growth, differentiation, apoptosis and metabolism<sup>3 5 18 19</sup>.

**Figure 1. Vitamin D Synthesis and Metabolism<sup>20</sup>**



### ***Vitamin D Deficiency***

Various thresholds for vitamin D deficiency have been defined<sup>1</sup>. The FCN classification is outlined in **Table 1**.

**Table 1. Serum 25(OH)D Concentrations and Classifications <sup>1</sup>**

<b>Classification</b>	<b>Serum 25(OH)D nmol/l (ng/ml)</b>	<b>Clinical Implications</b>
Vitamin D deficiency	< 50 nmol/l (< 20 ng/ml)	Summarizes both concentrations of severe deficiency and insufficiency
Severe vitamin D deficiency	< 25 nmol/l (< 10 ng/ml)	Increased risk of rickets, osteomalacia, secondary hyperparathyroidism, myopathy, falls, fractures
Vitamin D insufficiency	25 to 49 nmol/l (10 to 19 ng/ml)	Increased risk of bone loss, secondary hyperparathyroidism, falls, fractures
Adequate vitamin D threshold concentrations*	50 nmol/l (20 ng/ml)	Low risk for bone loss and secondary hyperparathyroidism, neutral effect on falls and fractures
Desirable vitamin D threshold concentrations for fall and fracture reduction**	75 nmol/l (30 ng/ml)	Optimal suppression of parathyroid hormone and bone loss; reduction of falls and fractures by about 20%

\* Threshold supported by the Institute of Medicine as adequate concentration for most people (97%).

\*\* Threshold supported by the Institute of Medicine (2010), International Osteoporosis Foundation (2010) and the US Endocrine Society (2011) for the reduction of falls and fractures, especially among older adults age 60+ years

### **Symptoms of Vitamin D deficiency**

Bone pain and muscle weakness, two symptoms associated with vitamin D deficiency, are rarely mentioned by the patient to the physician or recognized by the physician as being due to vitamin D deficiency <sup>5</sup>. In adults, prolonged vitamin D deficiency is known to contribute to or exacerbate osteoporosis <sup>5</sup>. Besides bone pain, the clinical presentation of osteoporosis is low trauma or spontaneous bone fractures. Prolonged vitamin D deficiency can also lead to osteomalacia in adults, characterized by bone softening and muscle weakness <sup>5</sup>. In children, prolonged vitamin D deficiency may cause brittle bones or rickets, the pediatric equivalent of osteomalacia caused by inadequate bone mineralization leading to soft bones and skeletal deformities <sup>5</sup>.

### **Vitamin D Supplementation and Vitamin D Testing**

Regarding to vitamin D testing, a distinction has to be made between the therapeutic setting and the preventive setting.

In a therapeutic setting, when suspecting a vitamin D deficiency, testing of vitamin D may have its role in the diagnosis and the evaluation of the response to treatment.

In the preventive setting, vitamin D testing is questioned. Testing is not an explicit prerequisite for vitamin D supplementation and physicians can prescribe vitamin D supplementation in order to prevent a vitamin D deficiency. Individuals may also get vitamin D supplements from their pharmacist or start vitamin D supplementation at their own initiative. Several specialized societies advise against the routine

screening of vitamin D status and recommend a strategy of primary prevention of deficiency through universal low-dose vitamin D supplementation for all young children and pregnant women <sup>21-24</sup>.

Supplementation with a dose of 600 to 800 IU of vitamin D per day is recommended for adults. Risks of overtreatment with vitamin D appear to be low and related immediate adverse effects (i.e. poisoning) are reported rarely <sup>25-27</sup>. Most studies of vitamin D supplements have used doses of 400–1000 IU/day, have not been associated with evidence of adverse effects, and it is generally held that doses up to 2000 IU/day are safe <sup>28</sup>. However, recent literature has shown that high intermittent vitamin D supplementation (bolus doses) can increase the risk of falls and fractures <sup>29</sup>.

Vitamin D supplementation with or without calcium has been associated with various positive effects on health outcomes, in particular with respect to falls and fractures in elderly <sup>30 31</sup>, muscle strength<sup>32</sup>, bone density <sup>33</sup> and physiological function <sup>34</sup>, type 2 diabetes mellitus <sup>35 36</sup>, gestational diabetes <sup>37</sup>, some types of cancer <sup>35 38-41</sup> but not all <sup>42 43</sup>, overall mortality <sup>44</sup> as well as cancer-related mortality <sup>43</sup>. Some studies report an effect on cardiovascular diseases <sup>45 46</sup> whereas some others do not <sup>42 47</sup>.

Although vitamin D supplementation with 800 IU per day is a recommended clinical practice, the benefits of compulsory testing in risk groups prior to supplementation remain unknown. One interest in vitamin D testing may be monitoring adherence to vitamin D supplementation.

## **4. Technology**

### **4.1. Technology Description**

The vitamin D status of an individual can be determined on a regular blood draw by measuring serum concentrations of 25-hydroxyvitamin or of 1,25-dihydroxyvitamin D <sup>48 49</sup>. Compared to 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D has a short circulating half-life and lower serum concentrations, making it more difficult to measure. However, the level of 1,25-dihydroxyvitamin D still needs to be determined in some cases, such as renal failure, granuloma disorders as well as in some rare inborn errors of metabolism <sup>48</sup>.

There are different techniques available for measuring the serum levels of both forms of vitamin D (e.g. enzyme immunoassay, radioimmunoassay, high-performance liquid chromatography, liquid chromatography-mass spectrometry and liquid chromatography-tandem mass spectrometry) <sup>48 50 51</sup>.

### **Recommendations of the Federal Commission of Nutrition on Vitamin D Testing**

In Switzerland, FCN recommends vitamin D testing in individuals at high risk for severe vitamin D deficiency (<25 nmol/L). The FCN recommends vitamin D supplementation in all individuals with serum vitamin D levels below 50 nmol/L<sup>1</sup>. Subpopulations considered to be at high risk of severe vitamin D deficiency according to the FCN, are listed in **Table 2**. The FCN developed this list of subpopulations<sup>1</sup> by adapting the list of groups at high risk of severe vitamin D deficiency provided by the US Endocrine Society<sup>21</sup>. No evidence is referenced by the FCN in their recommendation on testing<sup>1</sup>.

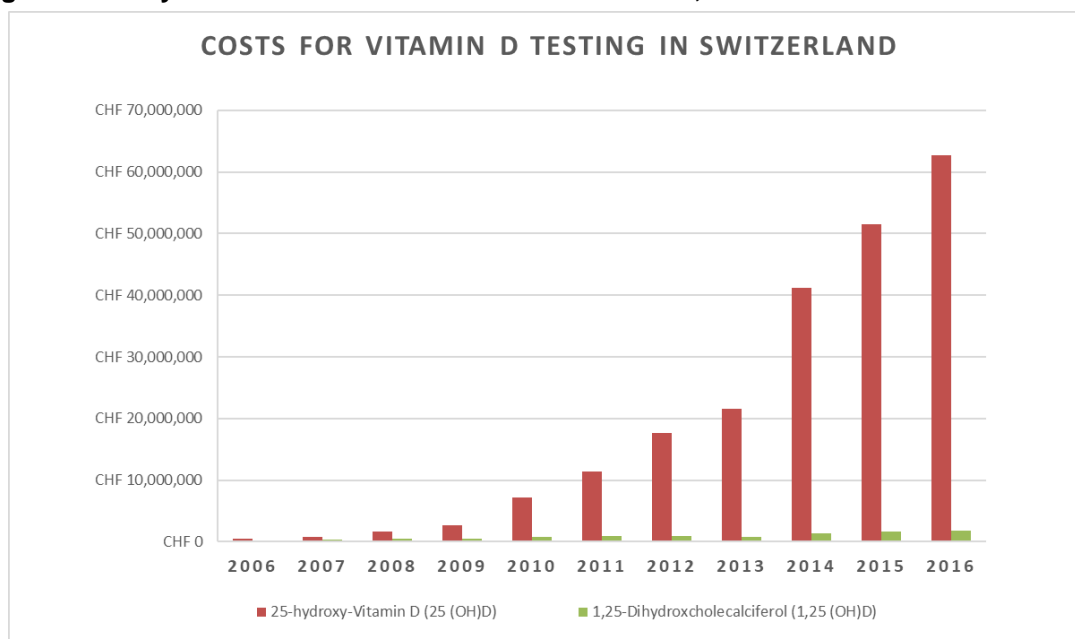
**Table 2. Subject Groups at High Risk of Severe Vitamin D Deficiency according to FCN<sup>1</sup>**

<b>Group</b>	<b>Specification</b>
Bone disorders	Rickets, osteomalacia, osteoporosis, any low trauma fracture, hyperparathyroidism
Older adults	With a history of a fall, with a history of low trauma fracture
Obese individuals	Adults (BMI 30 kg/m <sup>2</sup> or more), obese children with additional risk factors/symptoms
Pregnant and lactating women with risk factors or unwilling to take vitamin D supplements	Pregnant women with dark skin tone, obesity, gestational diabetes, minimal sun exposure, pregnant women not taking vitamin D supplements
Children and adults with a dark skin tone	African, Indian or Hispanic ethnicity
Athletes of all ages	Who primarily exercise indoors, or perform their regular outdoor training in early morning or late afternoon hours with minimal sunshine intensity
Chronic kidney disease	
Hepatic failure	
Malabsorption syndromes	Cystic fibrosis, inflammatory bowel disease, Crohn's disease, bariatric surgery, radiation enteritis
Medications	Antiepileptic medications, glucocorticoids, AIDS medications, antifungals, cholestyramine
Granuloma forming disorders	Sarcoidosis, tuberculosis, histoplasmosis, berilliosis, coccidiomycosis

### **Costs of Vitamin D Testing**

In various countries, vitamin D testing has increased significantly over the last years<sup>52-54</sup>. In Switzerland, the number of vitamin D tests has increased from about 9'500 in 2006 to about 1'179'000 in 2016. This increase is associated with a rise in costs to about CHF 60 million in 2016 (**Figure 2**, Source: SASIS Tarifpool).

**Figure 2. Yearly Costs for Vitamin D Tests in Switzerland, 2006 - 2016**



### **Coverage Policy of Vitamin D Testing**

In Switzerland, the laboratory analyses for vitamin D reimbursed by the compulsory health insurance<sup>55</sup> are listed on the Analysenliste (list of laboratory analyses, annex 3 of the Krankenpflege-Leistungsverordnung [KLV, SR 832.112.31]). The list contains 1,25-dihydroxy-cholecalciferol (position 1000.00) and the 25-hydroxy-vitamin-D (position 1006.00)<sup>56</sup>. The position 1006.00 includes the measurement of the total level of serum vitamin D (vitamin D2 plus vitamin D3). Even if the level of vitamin D2 and D3 are not measured simultaneously, the position 1006.00 can be only billed once on behalf of the compulsory health insurance<sup>56</sup>. At present the reimbursement by the compulsory health insurance of vitamin D testing is not restricted to specific risk groups.

In some countries, such as Canada, France or Germany, the reimbursement of vitamin D testing by health insurances has been limited to certain risk groups. For example, in Ontario, Canada, vitamin D testing reimbursement is restricted to persons with osteoporosis and osteopenia, rickets, malabsorption syndromes, renal disease, or persons on medications that affect vitamin D metabolism<sup>57</sup>. In Alberta, Canada, the introduction of an additional criterion requiring clinicians to identify the medical indication for vitamin testing in a patient, led to a 92% reduction in the number of vitamin D tests<sup>58</sup>.

In France, vitamin D testing reimbursement is restricted to persons with rickets or osteomalacia, older adults with recurrent falls, monitoring of kidney transplant in adults and persons who have undergone bariatric surgery<sup>59</sup>.

In Germany, the statutory health insurance covers the vitamin D testing only if the medical necessity is given<sup>60</sup>. Medical necessity is not further defined. The presence of a chronic disease such as bronchial



asthma or multiple sclerosis is not a reason for vitamin D testing coverage, but clinically manifest rickets or osteomalacia are.

#### **4.2. Alternative Technologies**

An alternative to vitamin D testing all subjects at high risk of severe vitamin D deficiency, as recommended in the 2012 FCN report <sup>1</sup>, is supplementing all high-risk individuals without prior vitamin D testing.

### **5. HTA key questions**

The aim of this scoping report is to explore a central research question (CRQ) on vitamin D testing; and also to explore an upstream research question (URQ) on vitamin D supplementation to select the appropriate target groups for the CRQ.

In order to evaluate the utility of vitamin D testing in a full HTA, one central research question and an upstream research question are formulated.

The central research question (CRQ) investigates:

- the clinical utility and economic impact of vitamin D testing in groups at high risk of severe vitamin D deficiency. Clinical utility is assessed in CRQa and economic impact in CRQb.

#### **5.1. Additional question**

The upstream research question (URQ) investigates:

- clinical effectiveness of vitamin D supplementation in the FCN-defined subpopulations at high risk of severe vitamin D deficiency.

### **6. PICOS**

**Table 3** shows the PICOS covering clinical utility and economic impact of vitamin D testing and the PICOS for vitamin D supplementation.

## 6.1. Populations

The different groups at high risk of severe vitamin D deficiency, as defined by the FCN <sup>1</sup>, form the different target populations for the CRQ and URQ. We did not consider any other populations than those defined in the FCN report. For instance, we did not consider populations with asthma, COPD or multiple sclerosis. Although these groups may also be considered as having a high risk of severe vitamin D deficiency, they were not defined in the FCN report from 2012.

Excluded are groups where vitamin D testing is medically necessary for diagnosing the following diseases: osteoporosis, rickets, osteopenia, malabsorption syndromes, renal and hepatic diseases or granuloma forming disorders. Persons using drugs affecting vitamin D metabolism, persons on chronic steroid medication, and persons under strict medical treatment such as persons post organ transplantation and persons with cancer, cardiovascular disease, metabolic disorders (e.g. diabetes) and sickle cell anaemia are also excluded. In these groups vitamin D testing is not being questioned. Also for children with symptoms <sup>1</sup>, or with an increased risk of vitamin D deficiency (e.g. children treated with classic anti-epileptics <sup>61</sup>, chronic intestine-, liver-, kidney diseases <sup>62 63</sup>, during glucocorticoid therapy <sup>64-66</sup> or need for osteoporosis prophylaxis), 25-OH-D-measurement should be performed <sup>67</sup>. The measurement of vitamin D levels in children at risk treated with pharmacological doses is advised to check correct dosage, compliance <sup>68</sup> and to prevent intoxications or nephrocalcinosis <sup>25</sup>.

## 6.2. Intervention

The technology of interest is vitamin D testing, and there is a CRQa for clinical evidence for vitamin D testing and a CRQb for economic evidence of vitamin D testing.

For the URQ vitamin D supplementation with or without calcium is the intervention. High dose intermittent vitamin D supplementation (bolus doses for >1 month) are excluded, as depicted in the PICOS-Box in **Table 3**. High intermittent vitamin D supplementation has been associated with an increased risk of falls and fractures <sup>28</sup>. This is why bolus studies of vitamin D supplementation have been excluded. It was beyond the scope of this report to consider certain factors, which may modify the effectiveness of vitamin D supplementation such as adherence and dosage, but we did consider the effect of co-administration of vitamin D with calcium. See keyword search strings for more details (**Appendices 1-3**).

## 6.3. Comparator

The technology chosen as comparator is no vitamin D testing/screening and /or vitamin D supplementation without prior testing of vitamin D for CRQa and CRQb.

For the URQ the comparator is no vitamin D supplementation, which means placebo, no treatment or regular care for the URQ, as depicted in the PICOS-Box in **Table 3**. See keyword search strings for more details (**Appendices 1-3**).

## 6.4. Outcomes

Clinical health outcomes for vitamin D testing and vitamin D supplementation are divided in bone health-related and non-bone health-related outcomes. Outcomes related to bone health are e.g., rickets, osteomalacia, PTH (parathyroid hormone) concentrations, bone mineral density (BMD) or bone mineral content (BMC). Indirect bone health-related outcomes are fractures, muscle strength or physical performance. Non-bone health-related outcomes can vary for each group at high risk of severe vitamin D deficiency defined by FCN.

To address the CRQ, any health outcome is considered as depicted in the PICOS-Box in **Table 3**.

To address the URQ, critical health-related outcomes per risk group were selected by clinical experts as depicted in **Table 4**. A nutritionist was also consulted for feedback on the selection of outcomes.

## 6.5. Study Design

For the CRQ, any comparative study was eligible for inclusion in our review. For the URQ only umbrella reviews (UR), HTA reports, SRs (including Cochrane reviews) and MAs (including network MAs/indirect treatment comparisons) were eligible for inclusion in our review, as depicted in the PICOS-Box in **Table 3**.

**Table 3. PICOS-Box CRQ and URQ**

	<b>CRQa: Vitamin D Testing (Clinical)</b>	<b>CRQb: Vitamin D Testing (Economic)</b>	<b>URQ: Vitamin D Supplementation (Clinical)</b>
<b>P</b> opulation	<ul style="list-style-type: none"> <li>• persons with bone disorders*</li> <li>• older adults (<math>\geq 65</math> yrs)</li> <li>• obese individuals</li> <li>• pregnant and lactating women</li> <li>• individuals with dark skin</li> <li>• athletes</li> </ul>		
<b>I</b> ntervention	Vitamin D testing (clinical)	Vitamin D testing (economic)	Vitamin D supplementation with or without calcium (excluding high dose intermittent vitamin D supplementation (>1 month))
<b>C</b> omparator	No vitamin D testing/screening; vitamin D supplementation without prior vitamin D testing	No vitamin D testing/screening; vitamin D supplementation without prior vitamin D testing	No vitamin D supplementation (placebo or regular care)

<b>Outcomes</b>	Bone health-related outcomes Indirect bone health-related outcomes Non-bone health-related outcomes	Costs, QALYs, HRQoL, life years gained, ICER/ICURs, net or gross budget impact	Refer to <b>Table 4</b>
<b>Study designs</b>	HTA reports, SRs, Mendelian RCTs, MAs, RCTs, any other experimental comparative study design and observational studies	HTA reports, systematic reviews, economic evaluations, economic evaluations alongside clinical trials (EEACTS), costing studies, budget impact studies	Umbrella reviews (URs), HTA reports, SRs (including Cochrane reviews), Meta-analysis (MAs) (including network MAs/indirect treatment comparisons)

Key: HTA=health technology assessment, HRQoL = health related quality of life, ICER/ICUR=incremental cost-effectiveness ratio/cost-utility ratio, MA=meta-analysis, QALYs=quality adjusted life years, RCT=randomized controlled trial, SR=systematic review, UR=umbrella review, USA=United States of America

\* Caveat: Rickets, osteomalacia, osteoporosis, hyperparathyroidism and low trauma fracture need vitamin D testing for diagnostic reasons

**Table 4** describes the outcomes considered for the URQ, which were pre-selected by clinical experts.

**Table 4. Outcomes Considered in the Review of Clinical Evidence of Vitamin D Supplementation (URQ)**

<b>Population:</b>	<b>Outcomes considered not bone related</b>	<b>Outcomes considered bone related</b>
<ul style="list-style-type: none"> <li>• Persons with bone disorders</li> <li>• Older adults (≥ 65yrs)</li> <li>• Obese individuals</li> <li>• Individuals with dark skin</li> <li>• Athletes</li> </ul>	<ul style="list-style-type: none"> <li>• Physical Performance</li> <li>• Muscle strengths</li> <li>• Falls</li> <li>• Injury</li> <li>• Pain</li> <li>• Mortality (all-cause or cancer related)</li> </ul>	<ul style="list-style-type: none"> <li>• Fractures (stratified; e.g. vertebral, non-vertebral)</li> <li>• Bone Mineral Density</li> </ul>
<ul style="list-style-type: none"> <li>• Pregnant and lactating women</li> </ul>	<ul style="list-style-type: none"> <li>• Preeclampsia</li> <li>• Maternal gestational diabetes</li> <li>• Preterm births</li> <li>• Low birth weight</li> </ul>	<ul style="list-style-type: none"> <li>• Fractures (stratified; e.g. vertebral, non-vertebral)</li> <li>• Bone Mineral Density</li> </ul>

## 7. Systematic Search Strategy

**7.1. Outcomes** A systematic literature search was conducted to extract the available evidence investigating clinical and economic effects of vitamin D testing in various groups at risk. A synthesis of the evidence is presented. A summary and an analysis of the individual outcomes are the objective of a full HTA, if commissioned.

Furthermore, a systematic literature search was conducted to extract the available evidence investigating which group(s) at risk profit from vitamin D supplementation in terms of improved bone-related or non-bone-related outcomes. In addition to extracting and synthesizing the evidence, the outcomes are summarized.

The selected evidence for vitamin D testing (CRQ) and vitamin D supplementation (URQ) is presented in PRISMA flow diagrams in **Chapter 8**, summarized descriptively in **Chapter 9** and presented in tables showing the characteristics and results of the studies in **Chapter 13**.

### 7.2. Search Strategy and Procedure: Effectiveness

Three systematic literature search strategies are followed to address CRQa and CRQb, as well as the URQ.

**Search Strategy 1:** CRQa for clinical evidence of vitamin D testing

**Search Strategy 2:** CQRb for economic evidence of vitamin D testing

**Search Strategy 3:** URQ for clinical evidence of vitamin D supplementation

**Search Strategy 1: CRQa.** The searches for clinical evidence for CRQa were performed on 15th January 2019 using MEDLINE (OVID), EMBASE (OVID), Centre for Reviews and Dissemination (CRD) database, the Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) and Epistemonikos.

**Search Strategy 2: CQRb:** The search for economic evidence for CRQb was performed on 4th January 2019 using MEDLINE (OVID), EMBASE (OVID) and the Centre for Reviews and Dissemination (CRD) database. Details on keyword search strings and use of search filters are presented in **Appendices 1-3**.

**Search Strategy 3: URQ:** The searches for clinical evidence for URQ were performed on 15th January 2019 using MEDLINE (OVID), EMBASE (OVID), Centre for Reviews and Dissemination (CRD) database, the Cochrane Central Register of Controlled Trials (Cochrane CENTRAL) and Epistemonikos.

### 7.3. Inclusion and exclusion criteria

Studies were included when they were published between January 2000 and January 2019. This was because two experts in the field of nutrition confirmed to us that literature on vitamin D supplementation representing the groups at high risk of severe vitamin D deficiency defined by the FCN only started being published from 2000 until December 2018. Only English language studies were considered (as most published scientific literature is in English); therefore, we may have missed relevant literature in other languages. Studies with vitamin D supplementation in combination with calcium were included. On the other hand, studies with bolus dose vitamin D supplementation (i.e. high dose intermittent vitamin D supplementation (>1 month)) were excluded. Also, other forms of vitamin D fortification as an intervention were excluded. Differences between the three search strategies regarding different interventions, outcomes and study types are described in **Table 3**. Although for CRQa and the URQ Cochrane CENTRAL and Epistemonikos were searched, these databases were not searched for the review of economic studies (CRQb).

### 7.4. Screening and selection procedure

A total of six reviewers conducted the 1<sup>st</sup> level screening of all titles and abstracts. A minimum of 5% of the literature was screened in duplicate, prior to single screening. Single screening was only started after confirmation of high agreement (>95%) between the pairs of reviewers. The full selection of titles and abstracts were screened with a focus on the FCN-defined at-risk groups described in **Table 3**. Titles and abstracts that are deemed appropriate from 1<sup>st</sup> level of screening as they demonstrated possibility of satisfying the PICOS criteria in Table 3, underwent full-text screening. Discrepancies between reviewers were double screened by other members of the review team. Resulting articles were selected for data extraction.

Only for **Search Strategy 3: URQ (clinical evidence of vitamin D supplementation)**, an additional selection procedure was applied, given the large body of available evidence. Strict criteria were applied to select studies in a transparent and reproducible manner. The criteria include:

- Only considering the outcomes paired to the relevant risk group (henceforth referred to as “outcome-risk group pairs”; e.g. falls in older adults) listed in **Table 4**.
- After full-text screening, all umbrella reviews (URs) which addressed a relevant outcome-risk group pair were included. URs specifically refer to reviews compiling evidence from multiple reviews into one accessible and useable document. URs focus on broad conditions or problems for which there are competing interventions. This is done by highlighting reviews that address

these interventions and their results<sup>69</sup>. We classified as URs reports, which focus on identifying systematic reviews and synthesizing their results.

- Only if no UR for an outcome-risk group pair was identified, we included all Cochrane reviews that were identified as addressing the outcome-risk group pair.
- Only if no UR or Cochrane review for an outcome-risk group pair was identified, we included the most recent SR addressing the outcome-risk group pair. If the most recent SR was of a low quality rated by the Assessing Methodological Quality of Systematic Reviews (AMSTAR) checklist<sup>70</sup>, we additionally included the second most recent SR addressing the outcome-risk group pair if available.

For the URQ only, we may have excluded some relevant studies assessing bone mineral density as an outcome during titles and abstracts screening. This is because we originally did not plan to include bone mineral density as an outcome for the URQ but only decided to do this after titles and abstracts screening.

### **7.5. Search Strategy and Procedure legal, ethical, social and organizational issues**

The systematic literature search in this scoping report did not address evidence pertaining to legal, ethical, social and organizational issues related to the HTA topic. This search will be performed in the HTA report, if commissioned.

## **8. Synthesis of Evidence Base**

### **8.1. PRISMA Flow Diagram**

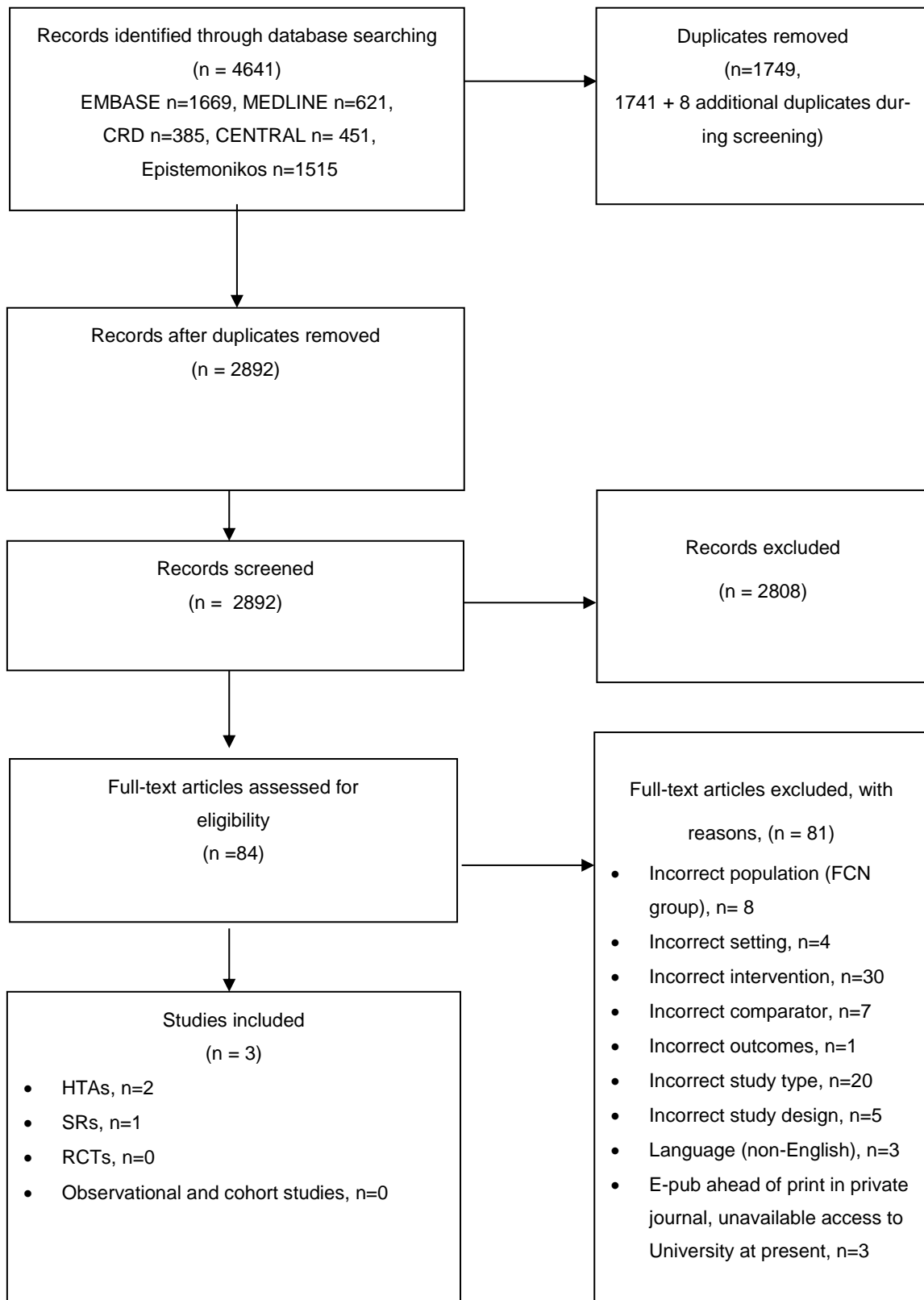
PRISMA flow diagrams for the three search strategies are presented in this section in accordance with the PRISMA guidelines<sup>71</sup>.

#### **8.1.1. Vitamin D Testing (Clinical; CRQa)**

The systematic literature search identified 4,641 studies of which 1,749 were duplicates. Titles and abstracts screening resulted in 84 studies for full text screening. In the full text screening, 81 studies were excluded; the reasons for excluding these studies are presented in the PRISMA diagram in **Figure 3** and listed in **Appendix 9**. Three studies (one SR<sup>72</sup> and two HTAs<sup>73 74</sup>) were included in the final review.

The characteristics of the selected studies are presented in **Appendix 4**. The findings of the studies are described in **Chapter 9**.

**Figure 3. PRISMA Diagram, Vitamin D Testing (Clinical; CRQa)**

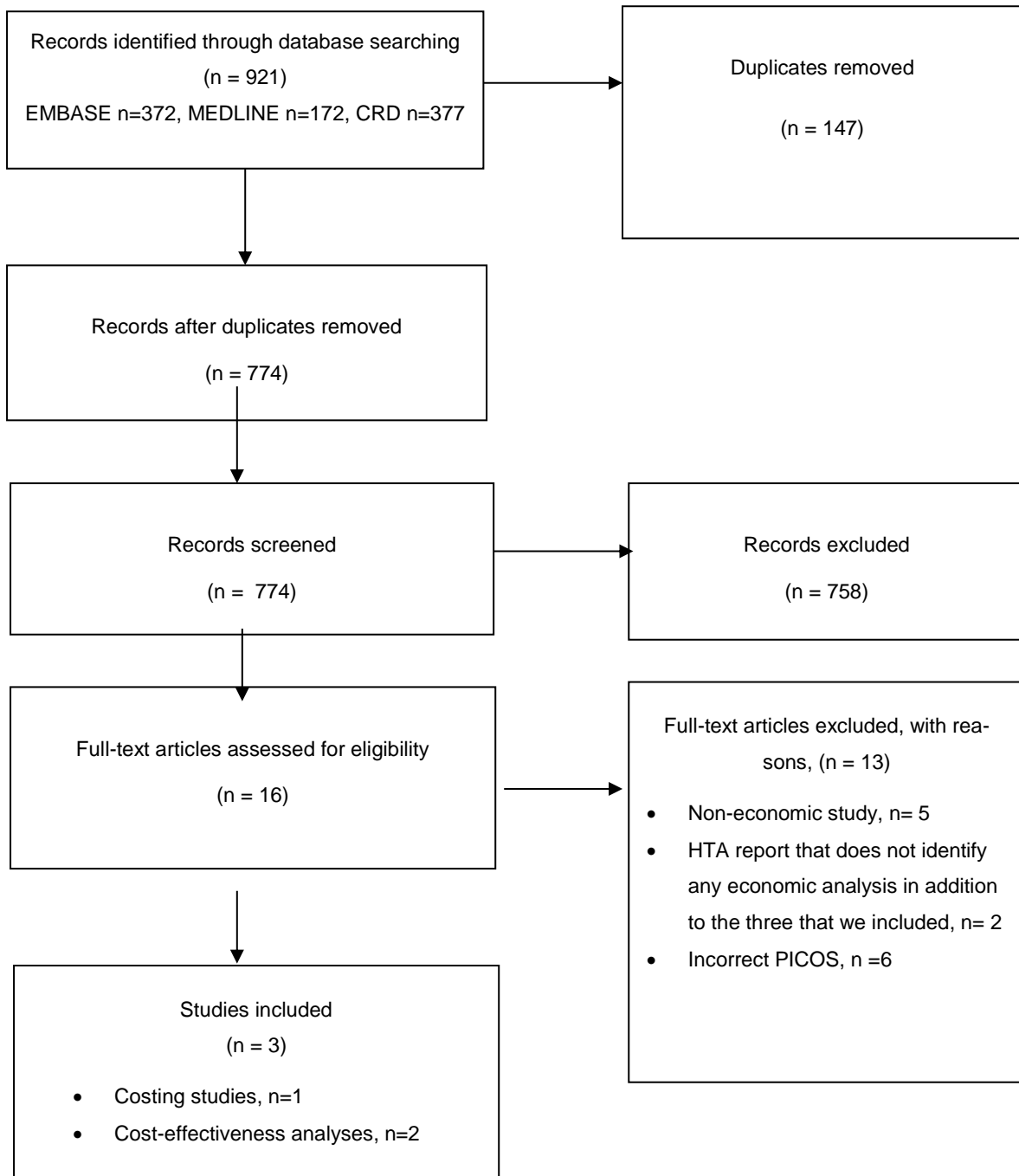




### 8.1.2. Vitamin D Testing (Economic, CRQb)

The systematic literature search identified 921 studies of which 147 were duplicates. Titles and abstracts screening resulted in 16 studies for full text screening. In the full text screening, 13 studies were excluded; the reasons for excluding these studies are presented in the PRISMA diagram in **Figure 4** and listed in **Appendix 10**. Three studies were included in the final review.

**Figure 4. PRISMA Diagram, Vitamin D Testing (Economic)**



The literature search identified three economic analyses <sup>24 75 76</sup>. Characteristics of the selected studies are tabulated in **Appendix 5** and results in **Appendix 6**. Findings are described in **Chapter 9**.

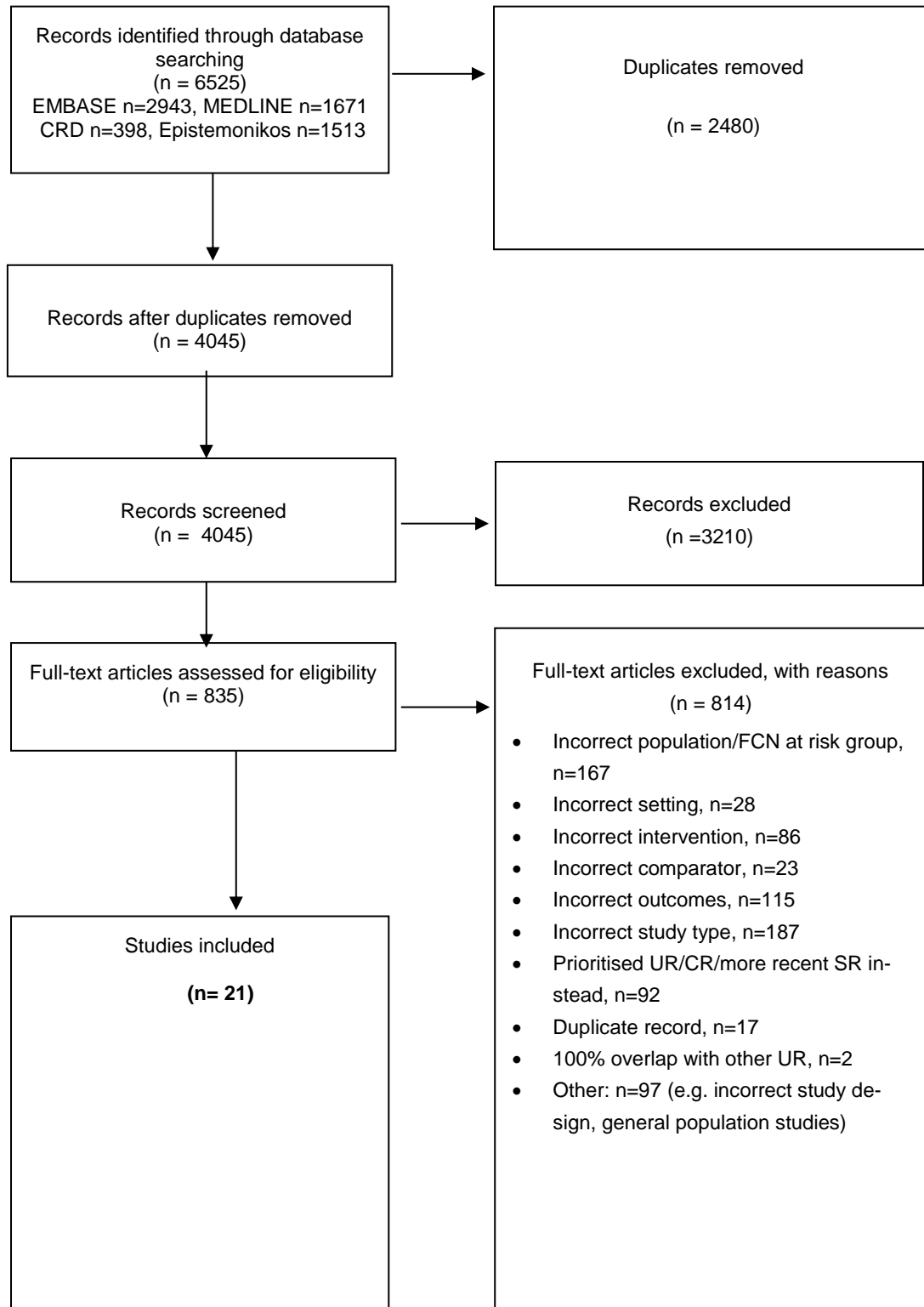
### 8.1.3. Vitamin D Supplementation (URQ)

The systematic literature search identified 6,525 studies of which 2,480 were duplicates. Titles and abstracts screening resulted in 835 studies for full text screening. In the full text screening, 813 were excluded; the reasons for excluding these studies are presented in the PRISMA diagram in **Figure 5** and listed in **Appendix 11**. 21 studies were included in the final review. Characteristics of the selected studies are tabulated in **Appendix 7** and results in **Appendix 8**.

We used the AMSTAR checklist only for the URQ, to assess the quality of the URs and SRs identified from the URQ systematic literature search. We agreed to use the following AMSTAR scoring classification specified by the Canadian Agency for Drugs and Technologies in Health (CADTH): low quality review (score 0 to 3), medium quality (score 4 to 7), and high quality (score 8 to 11) <sup>70</sup>. Quality of the reviews was generally assessed as high for pregnant women (median AMSTAR score of 11), medium for older adults (median AMSTAR score of 6), athletes (median AMSTAR score of 6) and persons with bone disorders (median AMSTAR score of 5), and low for obese individuals (median AMSTAR score of 2). AMSTAR scores assessed for each individual review that we included for the URQ, are presented in **Appendix 8**.

Our study selection procedure meant that we focused on umbrella reviews for the majority of outcomes, and only included systematic reviews where an umbrella review was not identified. Such a procedure may mean that we excluded recently published systematic reviews of relevance. In comparison with a full-scale, much more resource-intensive systematic review approach, a certain risk of bias is implied. Furthermore, some umbrella or systematic reviews could be classified into both the bone disorders and in the older adults groups. In these cases, we assigned the review to the bone disorders group if the authors stated a focus of their review was on persons with a bone disorder or especially high risk of having a bone disorder, and otherwise assigned the review to the older adults group. Furthermore, we classed Bolland et al (2018) as an UR <sup>77</sup>. Although they looked at individual trials, they also synthesized previously published meta-analyses. For data extraction of Bolland et al (2018) <sup>77</sup>, we only extracted the results of the subgroup analyses focused on daily vitamin D supplementation (and therefore excluded trials of bolus vitamin D supplementation). The methodological quality of the review by Bolland et al has been questioned <sup>78</sup>. Bolland et al excluded all trials that compared combined vitamin D and calcium supplementation, with placebo.

**Figure 5. PRISMA Diagram, Vitamin D Supplementation**



## 9. Findings

### 9.1. Findings of Vitamin D Testing

#### 9.1.1. Clinical effectiveness of vitamin D testing (CRQa)

Three studies were identified, which were published between 2012 and 2015. The three studies included one SR (LeBlanc et al (2015) <sup>72</sup>), two HTA reports (CADTH 2014a <sup>73</sup>, CADTH 2014b <sup>74</sup>) and zero empirical studies. LeBlanc et al (2015) conducted a systematic search for randomized trials of the clinical effectiveness of vitamin D testing versus no testing, and found zero randomized trials evaluating this <sup>72</sup>. CADTH (2014a) conducted a systematic search for empirical studies of the clinical effectiveness of vitamin D testing in northern populations, and found zero empirical studies evaluating this <sup>73</sup>. CADTH (2014b) conducted a systematic search for empirical studies of the clinical effectiveness of vitamin D testing in the general population, and found one empirical study evaluating this, but the study had a retrospective design thus was not eligible for our report <sup>74</sup>.

*In summary, we could not identify any randomized trial-based evidence on vitamin D testing.*

#### 9.1.2. Costs and cost-effectiveness of vitamin D testing (CRQb)

We identified one costing study and two cost-effectiveness studies of vitamin D testing; findings are summarized below and described and tabulated in **Appendix 6**.

##### **Costs and budget impact**

A HTA published in 2015, reported a UK costing and budget impact study conducted by the York Health Economics Consortium (YHEC) for a submission to NICE (National Institute of Health and Care Excellence) <sup>24</sup>. The target populations (aligned with groups at high risk of severe vitamin D deficiency as defined by the FCN) were older people (aged 65 and over) and people with darker skin. Assessed were costs and budget impact of vitamin D testing in risk groups and subsequent daily 3000 IU vitamin D supplementation for those deficient (vitamin D testing and treatment strategy for the deficient), and vitamin D supplementation of daily 1000 IU without prior vitamin D testing within each risk group (no vitamin D testing and supplementation strategy for all). For older people as well as for people with darker skin, overall costs were estimated to be lower if supplementation of vitamin D without prior vitamin D testing was given instead of implementing the vitamin D testing and treatment strategy.

Vitamin D testing all UK persons aged 65 or above (population size of 9,176,882 of which 11% were assumed in the study to be vitamin D deficient), was estimated to result in higher (incremental) costs of GBP 25,359,122 relative to providing vitamin D supplementation without prior vitamin D testing for these

people. Vitamin D testing all UK persons with dark skin (population size of 15,733,034 of which 69% were assumed in the study to be vitamin D deficient), was estimated to result in higher (incremental) costs of GBP 160,181,034 relative to providing vitamin D supplementation without prior vitamin D testing for these people.

### **Cost-effectiveness**

A USA economic evaluation by Lee et al in 2012 assessed the cost-effectiveness of selective vitamin D supplementation following a vitamin D test, versus vitamin D supplementation without prior vitamin D testing, or no vitamin D supplementation, in older women and men (65-80) <sup>75</sup>. Effectiveness estimates were based on a MA of vitamin D supplementation (rather than vitamin D testing) showing that vitamin D supplementation reduces the risk of falls, although Lee et al did not precisely state which MA they used to parameterize the economic model. Costs and quality-adjusted life years (QALY) were evaluated over a 3-year period. A willingness-to-pay threshold of USD 50,000 per QALY gained was used. For females aged 65-80 years the vitamin D testing and supplementation strategy was 52.8% likely to be the most cost-effective strategy (as 52.8% of simulations in the probabilistic sensitivity analysis indicated the highest net monetary benefit was for this strategy), compared to 36.3% probability for the vitamin D supplementation without prior vitamin D testing strategy. Using the same threshold for males aged 65-80 years, vitamin D testing and supplementation was 54.3% likely to be the most cost-effective strategy compared to just 38.2% probability for the vitamin D supplementation without prior vitamin D testing strategy. The authors did not estimate incremental cost-effectiveness ratios (ICERs).

The French economic evaluation by Zarca et al in 2014 <sup>76</sup> assessed the cost-effectiveness of:

i) vitamin D testing all older adults aged  $\geq 65$  years without previous hip fracture followed by vitamin D supplementation of those measured as vitamin D deficient

and ii) vitamin D supplementation of all older adults without previous hip fracture followed by a test three months after initiation and subsequent treatment adaptation for older adults aged  $\geq 65$  years without a previous hip fracture.

Effectiveness estimates were based on two MAs of vitamin D supplementation (rather than vitamin D testing), which indicated vitamin D supplementation reduces hip fracture risk <sup>79 80</sup>. Costs and QALYs were evaluated over the lifetime of the individuals. It was found that for a willingness-to-pay threshold of over EUR 6,000 per QALY, the strategy of vitamin D testing all older adults without previous hip fracture followed by vitamin D supplementation of those measured as vitamin D deficient (strategy (i)) was the most likely strategy to be cost-effective. Strategy (i) produced an ICER of €5,219 per QALY compared to no vitamin D supplementation.

*In summary, economic results for testing in older adults were mixed and non-conclusive. For older adults as well as for people with darker skin, overall costs were estimated to be lower if supplementation of vitamin D without prior vitamin D testing is given, in comparison with a strategy of vitamin D testing and treatment for the deficient.*

*Conversely, both cost-effectiveness studies that we identified reported that initial vitamin D testing in older adults and subsequent supplementation for the deficient was more cost-effective than initial vitamin D supplementation for all older adults. Both these cost-effectiveness studies based their effect estimates on meta-analyses which indicated vitamin D supplementation is effective at improving falls and fracture outcomes.*

## **9.2. Findings of Vitamin D Supplementation (URQ)**

Study findings in a tabulated format are presented in **Appendix 8**.

### **9.2.1. Descriptive Presentation**

**Table 4** refers to more outcomes than are reported in this section, as there were no SRs for some outcomes. For persons with bone disorders, we only identified reviews addressing fracture and BMD outcomes. For obese individuals, we only identified reviews addressing BMD outcomes. For athletes, we only identified reviews addressing injury, physical performance and muscle strength outcomes. For persons with dark skin, we did not identify any reviews addressing the outcomes listed in **Table 4**.

#### ***FCN Group 1: Persons with Bone Disorders***

This section describes the results of the reviews focusing on older adults who have a bone disorder or especially high risk of acquiring one. The studies identified included populations with high fracture risk, low BMD/osteoporosis and previous hip fracture. The effects of vitamin D supplementation may differ in such persons compared to general populations of older adults. URs/SRs focusing on patients with a pre-existing history of osteomalacia or rickets were not identified. We found fewer studies on vitamin D supplementation in older adults with bone disorders, and they involved smaller sample sizes than studies in general populations of older adults.

**Fractures (people with high fracture risk).** An UR by Maclean et al (2008) <sup>81</sup> assessed effects of vitamin D supplementation relative to placebo on the fracture risk in people with a high risk of fracture (e.g. 50% of trial participants with previous osteoporotic fracture at baseline). In the UR, two SRs were identified for vertebral fracture published by Avenell et al (2005) <sup>82</sup> and Stevenson et al (2005) <sup>83</sup>. They involved 2745 and 109 participants in the pooled analyses, respectively. Both reported no significant

effects for vertebral fracture (RR of vitamin D supplementation versus placebo=3.97 (95% CI: 0.44 to 35.45) in Avenell et al (2005); RR of vitamin D supplementation versus placebo=1.02 (95% CI: 0.44 to 2.32) in Stevenson et al (2005)). In the UR, one SR was identified for non-vertebral fracture published by Stevenson et al in 2005<sup>83</sup> (213 participants), which reported no significant effect (RR not numerically reported but depicted as non-significant in forest plot). In the UR, one SR was identified for hip fracture (updated in 2014 by Avenell et al with 2820 participants<sup>84</sup>), which reported no significant effect (RR of vitamin D supplementation versus placebo=1.08 (95% CI: 0.72 to 1.62)) in 2014 update.

**Fractures (people with low bone density or osteoporosis).** A SR by Qaseem et al (2017)<sup>85</sup> evaluated 68 studies on vitamin D supplementation alone (without calcium) in persons with low bone density or osteoporosis, and assessed that the effect on fracture risk was uncertain due to mixed findings across MAs/RCTs; the authors evaluated the quality of the studies to be of a moderate quality from GRADE assessment.

**Second fracture (persons after first hip fracture).** A SR by Egan et al (2008) identified one relevant RCT including 76 participants of the effect of vitamin D plus calcium supplementation on the risk of second hip fracture in persons recovering from their first hip fracture<sup>86</sup>. Over 12 months, 8% (n=3) of the vitamin D plus calcium group experienced a second fracture; whereas 14% (n=5) of placebo group experienced a second fracture. Due to the small sample size, the statistical significance of this difference between groups was not assessed.

**Bone mineral density (female elderly nursing home residents).** A SR by Parikh et al (2009)<sup>87</sup> identified three relevant RCTs on the effect of vitamin D supplementation on BMD in nursing home residents. All three RCTs comprised of female nursing home residents aged at least 79 years; thus the majority were likely to have osteoporosis. All three RCTs found that vitamin D plus calcium supplementation was associated with higher BMD outcomes after 18 to 24 months; however, confidence intervals were not reported.

*In summary, the evidence of effectiveness of vitamin D supplementation was generally mixed and sparse for persons with a bone disorder.*

### **FCN Group 2: Older Adults**

**Falls.** A total of three URs were identified assessing the effect of vitamin D supplementation alone on falls (Stubbs et al (2015a), Medical Advisory (2008) and Poscia et al (2018)). Stubbs et al (2015a)<sup>88</sup> and Medical Advisory (2008)<sup>89</sup> indicated no effect on falls resulting from vitamin D supplementation

alone. However, Poscia et al (2018)<sup>90</sup>, reported a reduction in falls in three of the SRs that they identified. Three URs were identified which assessed vitamin D co-administered with calcium (Stubbs et al (2015a)<sup>88</sup>, Poscia et al (2018)<sup>90</sup> and Medical Advisory (2008)<sup>89</sup>), all three indicated a resultant reduction in falls, although Medical Advisory (2008) found this reduction was evident for women only (RR=0.83 (95% CI: 0.73 to 0.95); 2,121 women from two trials)<sup>89</sup>. Four URs<sup>77 91-93</sup> were identified, which assessed mixed studies of vitamin D either alone or with calcium. Of these one UR<sup>77</sup> reported a statistically significant reduction in falls from daily vitamin D supplementation with or without calcium (Bolland et al (2018) subgroup results, RR=0.92, 95% CI: 0.87 to 0.98). Another UR also indicated a reduction in falls from vitamin D supplementation with or without calcium (Scragg et al (2012))<sup>91</sup>, but the other two URs indicated no effect on falls from vitamin D with or without calcium (Theodoratou et al (2014)<sup>92</sup> and Stubbs et al (2015b)<sup>93</sup>). Only one UR on the effect of vitamin D supplementation with calcium on fall-related fractures or fall-related injuries was identified, which was published by Medical Advisory in 2008<sup>89</sup>. This UR reported a non-significant reduction in fall-related fractures (RR=0.77 (95% CI: 0.49 to 1.21), two studies of vitamin D and calcium, 3,980 participants) and fall-related injuries (RR=0.48 (95% CI: 0.12 to 1.84), one study, 148 women).

**Fractures.** Out of the two URs assessing vitamin D supplementation alone (Vestergaard et al (2011)<sup>94</sup> and Poscia et al (2018)<sup>90</sup>), both indicated no effect on fractures (either vertebral or non-vertebral). Out of the two URs identified assessing vitamin D co-administered with calcium (Vestergaard et al (2011)<sup>94</sup> and Poscia et al (2018)<sup>90</sup>), both indicated a reduction in fractures from supplementation, although Vestergaard et al<sup>94</sup> indicated that this reduction was evident for non-vertebral but not for vertebral fracture, both based on low-quality evidence. Out of the three URs identified assessing mixed studies of vitamin D supplementation either alone or with calcium, two indicated no effect on fractures (Theodoratou et al (2014)<sup>92</sup> and Bolland et al (2018) subgroup results)<sup>77</sup>, although the third UR (Scragg et al (2012))<sup>91</sup> indicated a reduction in some types of fractures.

**Muscle strength.** Two URs for muscle strength outcomes in older adults were identified published in 2018 and 2014, respectively. The 2018 UR was published by De Spiegeleer et al<sup>95</sup>, and identified two SRs by Anagnostis et al (2015) and Beaudart et al (2017). Evidence of improvement in muscle strength from vitamin D supplementation in women was observed in the review by Anagnostis et al<sup>96</sup>, but in the review by Beaudart et al<sup>97</sup>, no effect of vitamin D supplementation was found. The 2014 UR by Theodoratou et al<sup>92</sup> identified one MA comprising three RCTs that found non-significant improvement in lower extremity muscle strength from vitamin D supplementation (standardised mean difference=0.05 (95% CI: -0.11 to 0.20)).



**Physical performance.** Two URs for physical performance outcomes from vitamin D supplementation in older adults published in 2018 and 2014, were identified. The 2018 UR was published by De Spiegeleer et al <sup>95</sup> and identified two reviews (one UR and one SR); with the first review finding improvement in the timed-up-and-go test from vitamin D supplementation in 50% of included RCTs, and the second review reporting no improvement in gait based on studies of limited methodological quality. The 2014 UR was published by Theodoratou et al <sup>92</sup> and identified one MA comprising three RCTs that observed improvement (i.e. reduction) in the balance sway from vitamin D supplementation (standardised mean difference=-0.20 (95% CI: -0.39 to -0.01)).

**Bone mineral density.** Unlike the other outcomes in this section, which were based on a systematic search, we carried out a non-systematic search to identify SRs evaluating BMD. For older adults, one UR for a BMD outcome was identified which was published by Bolland et al in 2018 (subgroup results) <sup>77</sup>. In this UR, a subgroup meta-analysis of daily vitamin D supplementation was carried out by the authors, in which data was pooled from 18 RCTs. In the subgroup analysis, no statistically significant improvement in lumbar spine BMD from daily vitamin D supplementation was observed (weighted mean percentage difference=0.15% (95% CI: -0.13 to 0.44)).

**All-cause mortality.** The most recent UR we identified for all-cause mortality was from Poscia et al (2018) <sup>90</sup>. The UR concluded that vitamin D supplementation did not have a significant effect on all-cause mortality in a population of post-menopausal women and older men (for vitamin D supplementation alone compared with no vitamin D supplementation, RR=0.99 (95% CI: 0.94 to 1.03): for vitamin D co-administered with calcium supplementation compared with no vitamin D supplementation, RR=0.94 (95% CI: 0.87 to 1.02)). However, an UR by Scragg et al (2012) <sup>91</sup> identified two SRs which both indicated no statistically significant reduction in mortality when vitamin D is administered alone but a statistically significant reduction in mortality from supplementation when vitamin D is co-administered with calcium to people aged  $\geq 60$  years.

**Cancer-related mortality.** A Cochrane review by Bjelakovic et al (2014) <sup>98</sup> identified and pooled the results of four RCTs that included 44,492 participants in total, to assess the effect of vitamin D supplementation on cancer-related mortality in postmenopausal women and older men. The authors found that, based on moderate quality evidence, vitamin D3 statistically significantly decreased cancer mortality (RR=0.88 (95% CI: 0.78 to 0.98)).

**Pain.** A SR by Husebo et al (2016)<sup>99</sup> on the effect of vitamin D supplementation on pain in persons with dementia identified one relevant RCT, which found no significant effect of Vitamin D3 supplementation ( $p>0.10$  for all pain measures administered to persons with advanced dementia).

### ***Findings for subpopulations of older adults***

Stakeholders made us aware of the following three studies: Cameron et al (2018) <sup>100</sup>, Tricco et al (2017) <sup>101</sup> and Zhang et al (2019) <sup>102</sup>, which however were not eligible for inclusion according to our pre-defined selection criteria. We report these analyses due to concerns that effects may be stronger or better visible in some subpopulations of older adults. These studies include participants with mean age of  $\geq 65$  years for the main analysis.

A Cochrane review published by Cameron et al in 2018 <sup>100</sup> found, in a subgroup of participants in care facilities and hospitals, that vitamin D supplementation reduced the rate of falls (rate ratio=0.72 (95% CI: 0.55 to 0.95), 4,512 participants) but not the risk of falls (RR= 0.92 (95% CI: 0.76 to 1.12), 4,512 participants) or the risk of fractures (RR=1.09 (95% CI: 0.58 to 2.03), 4,464 participants).

A network meta-analysis published by Tricco et al in 2017 <sup>101</sup> found, in a subgroup of participants receiving vitamin D and calcium supplementation combined with clinic-level quality improvement strategies (e.g., case management) and multifactorial assessment and treatment (e.g., comprehensive geriatric assessment), that the study intervention reduced the risk of injurious falls (odds ratio=0.12 (95% CI: 0.03 to 0.55; 41,596 participants).

A systematic review published by Zhang et al in 2019 <sup>102</sup> found, in subgroups supplemented with different modes of vitamin D, that both, vitamin D2 (RR=1.03 (95% CI: 0.98 to 1.09), 17,544 participants), and vitamin D3 (RR=0.95 (95% CI: 0.90 to 1.00), 57,910 participants) did not reduce all-cause mortality. However, the authors reported that all-cause mortality was significantly lower in trials with vitamin D3 supplementation than in trials with vitamin D2 supplementation (P for interaction=0.04).

***In summary, the evidence of effectiveness of vitamin D supplementation was generally mixed for older adults.***

### **FCN Group 3: Obese Individuals**

**Bone mineral density (BMD).** Unlike the other outcomes in this review, which were based on a systematic search, we carried out a non-systematic search in July 2019 to identify SRs evaluating BMD. For obese individuals, a SR from Bassatne et al (2019) <sup>103</sup> performed a search from 2010 to 2018 and identified one RCT assessing the effect of vitamin D supplementation on BMD in obese individuals. The RCT administered vitamin D3, and observed no significant differences between groups regarding change in BMD.

*In summary, the evidence of effectiveness of vitamin D supplementation was generally sparse for obese individuals.*

#### **FCN Group 4: Pregnant Women**

**Pre-eclampsia.** An UR by Browne et al (2016) <sup>104</sup> identified one SR assessing pregnancy-related outcomes (e.g. pre-eclampsia, low birthweight, maternal gestational diabetes, preterm birth) from vitamin D supplementation in pregnant women. The SR was updated in 2019 by Palacios et al <sup>105</sup>. Both the original systematic review and its update in 2019, found zero RCTs on the effect of vitamin D supplementation on pre-eclampsia in a Western country.

**Low birthweight.** An UR by Browne et al (2016) <sup>104</sup> identified one SR assessing pregnancy-related outcomes from vitamin D supplementation in pregnant women. The SR was updated in 2019 by Palacios et al <sup>105</sup>, and the combined searches found one Western country trial on the effect of vitamin D supplementation on low birthweight, which reported no statistically significant effect (RR for vitamin D monotherapy relative to no intervention was 0.53 (95% CI: 0.23 to 1.21) based on a sample of 126 women).

**Maternal gestational diabetes.** An UR by Browne et al (2016) <sup>104</sup> identified one SR assessing pregnancy-related outcomes from vitamin D supplementation in pregnant women. The SR was updated in 2019 by Palacios et al <sup>105</sup>. Both the original systematic review and its update in 2019, found zero trials on the effect of vitamin D supplementation on maternal gestational diabetes in a Western country.

**Preterm birth.** An UR by Browne et al (2016) <sup>104</sup> identified one SR assessing pregnancy-related outcomes from vitamin D supplementation in pregnant women. The SR was updated in 2019 by Palacios et al <sup>105</sup>, and pooled the results of seven trials across developed and developing countries on the effect of vitamin D supplementation on preterm birth (< 37 weeks). The SR found the RR of a preterm birth of vitamin D monotherapy relative to no intervention was 0.66 (95% CI 0.34 to 1.30), and concluded that vitamin D monotherapy supplementation may make little or no difference in the risk of having a preterm birth based on low-certainty evidence.

**Offspring bone mineral content (BMC).** Unlike the other outcomes in this review, which were based on a systematic search, we carried out a non-systematic search to identify SRs evaluating BMC. For the offspring of pregnant women, a 2014 SR by Harvey et al <sup>106</sup> identified one RCT assessing the effect of vitamin D supplementation in pregnant women on offspring bone mineral content. There was no significant difference in the BMC of the forearms of babies born to these women between the intervention and comparator groups (mean bone mass outcome of 3.19 units at birth in the vitamin D and calcium group, 3.10 units at birth in the “no intervention” group; no p value reported). The SR also evaluated that the RCT had a high risk of bias.

**Maternal bone mineral density.** Unlike the other outcomes in this review, which were based on a systematic search, we carried out a non-systematic search to identify SRs evaluating BMD. For pregnant women, a SR by Cranney et al (2007)<sup>33</sup> was identified, and found zero trials on the effect of vitamin D supplementation in pregnant women on maternal bone mineral density.

**Maternal fractures.** We found one SR on the effect of vitamin D supplementation in pregnant women on maternal fractures, which was published by Cranney et al in 2007<sup>33</sup>, and identified zero trials.

*In summary, the evidence of effectiveness of vitamin D supplementation was generally sparse for pregnant women.*

#### **FCN Group 5: Children and Adults with a Dark Skin Tone**

No appropriate SR was found, but a future SR for which the protocol has been published (Cashman et al (2019))<sup>107</sup> may be of relevance.

#### **FCN Group 6: Athletes**

**Injury.** We identified a SR by Farrokhyar et al (2017)<sup>108</sup>, which found no RCTs evaluating the effect of vitamin D supplementation on injury in athletes.

**Physical performance.** We identified a SR by Farrokhyar et al (2017)<sup>108</sup>, which found seven RCTs evaluating the effect of vitamin D supplementation on physical performance outcomes in athletes. The SR found no significant improvement in physical performance from vitamin D supplementation, as no significant between-groups differences were found in vertical jump height (0.92 cm (95% CI:-0.55 to 2.44)), one repetition maximum (1-RM) bench press (2.05 (95% CI:-5.5 to 9.6)) or 10- to 30meters sprint (0.04 s (95% CI:-0.04 to 0.12)).

**Muscle strength.** We identified a SR published by Chiang et al (2017)<sup>109</sup> (rated low quality by AMSTAR), which found four trials evaluating the effect of vitamin D3 supplementation and two trials evaluating the effect of vitamin D2 supplementation on muscle strength. In the SR, vitamin D3 was shown to result in an improvement in muscle strength ( $p \leq 0.05$  in two trials; non-significant improvements in muscle strength in the other two trials). Vitamin D2 was found to be ineffective at impacting muscle strength in both trials ( $p > 0.05$  in each of the two trials).

*In summary, the evidence of effectiveness of vitamin D supplementation was generally mixed/sparse for athletes.*

## **10. Feasibility of HTA and Conclusions**

The focus of the present report was to identify studies, which have assessed the effect of vitamin D testing on clinical outcomes in selected FCN-defined risk groups, rather than to explore the mechanisms by which vitamin D testing may improve clinical outcomes.

In the systematic literature search, we found a lack of clinical evidence for vitamin D testing for persons with bone disorders, older adults, obese individuals, pregnant women, people with dark skin, and athletes, as we identified three reviews but no primary studies. Also, the study situation regarding the cost-effectiveness of vitamin D tests is limited. Therefore, conducting a full HTA on vitamin D testing could not be expected to yield additional, meaningful results.

In populations who are likely to have low vitamin D status, vitamin D testing may be helpful in promoting adherence to prescribed supplementation, and informing the correct vitamin D dosage. A vitamin D test is useful and necessary for risk groups if a differentiated vitamin D supplementation with individual saturation according to a pre-existing level of vitamin D deficiency is aimed for <sup>110</sup>. However, no definitive conclusions can be drawn about the effectiveness of vitamin D testing since no trials have been conducted to directly assess the impact of vitamin D testing on health outcomes (a previous HTA from the Washington State Health Care Authority in the USA in 2012 also came to this conclusion <sup>49</sup>).

Economic results for testing in older adults were mixed and non-conclusive.

In regards to vitamin D supplementation, we pursued a systematic but non-comprehensive approach to the literature search and selection, which carries a potential risk of bias. On this basis, the evidence on effectiveness of vitamin D supplementation was generally mixed and not conclusive.

We conclude that there is not sufficient evidence that would support the utility to test vitamin D in persons with bone disorders, older adults, obese individuals, pregnant women, people with dark skin, and athletes.

Vitamin D testing is recommended for patients where it is medically necessary, and this is not disputed in the present report. The lack of available evidence for vitamin D testing for defined at-risk groups from our review, could be informative in guiding a decision policy on vitamin D testing.

## 11. Outlook

The scoping report aims to map the existing literature in the field of interest in terms of the volume, nature, and characteristics of the primary research. The scoping report of a body of literature is used to analyse the complexity and/or heterogeneity of the topic. Based on the scoping report the feasibility to produce a full HTA has been estimated. A full HTA on vitamin D testing cannot be justified at present due to the absence of clinical studies evaluating the effectiveness of vitamin D testing. Only after such studies have become available can the topic be re-considered.

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### 13. Appendices

#### Appendix 1. Keyword Search Strings - Clinical Effectiveness of Vitamin D Testing

EMBASE Search Strategy- Clinical Effectiveness of Vitamin D Testing

Database(s): Embase 1974 to 2019 January 18		
Search Strategy:		
#	Searches	Results
1	exp screening/ or screening.mp. or testing.mp. or haematologic test*.mp. or hemotologic test*.mp. or haematological test*.mp. or hemotological test*.mp. or haematology test*.mp. or hematology test*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1628248
2	Clinical Trial/	953685
3	Randomized Controlled Trial/	531886
4	controlled clinical trial/	459983
5	multicenter study/	204931
6	Phase 3 clinical trial/	37466
7	Phase 4 clinical trial/	3248
8	exp RANDOMIZATION/	81027
9	Single Blind Procedure/	33669
10	Double Blind Procedure/	157181
11	Crossover Procedure/	57925
12	PLACEBO/	329135
13	randomi?ed controlled trial\$.tw.	194930
14	rct.tw.	30994
15	(random\$ adj2 allocat\$).tw.	38801
16	single blind\$.tw.	22236

17	double blind\$.tw.	194300
18	((treble or triple) adj blind\$.tw.	904
19	placebo\$.tw.	283766
20	Prospective Study/	496222
21	or/2-20	2076628
22	Case Study/	58701
23	case report.tw.	372301
24	abstract report/ or letter/	1091920
25	Conference proceeding.pt.	0
26	Conference abstract.pt.	3260356
27	Editorial.pt.	594275
28	Letter.pt.	1054905
29	Note.pt.	741015
30	or/22-29	6065154
31	21 not 30	1582846
32	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or colecalciferol).tw. or exp vitamin D/	144502
33	exp cohort analysis/ or exp longitudinal study/ or exp prospective study/	942069
34	research subjects/ or exp "clinical trial (topic)"/ or (research or trial? or study or studies or pilot or program\$ or longitudinal or prospective or retrospective).ti. or observational study as Topic/	2955073
35	exp Meta Analysis/	156343
36	((meta adj analy\$) or metaanalys\$.tw.	185093
37	(systematic adj (review\$1 or overview\$1)).tw.	166158
38	or/35-37	317284
39	cancerlit.ab.	725
40	cochrane.ab.	87227
41	embase.ab.	91334
42	(psychlit or psyclit).ab.	992
43	(psychinfo or psycinfo).ab.	24313
44	(cinahl or cinhal).ab.	26711

45	science citation index.ab.	3344
46	bids.ab.	613
47	or/39-46	142964
48	reference lists.ab.	17505
49	bibliograph\$.ab.	20726
50	hand-search\$.ab.	7449
51	manual search\$.ab.	4696
52	relevant journals.ab.	1314
53	or/48-52	46544
54	data extraction.ab.	21486
55	selection criteria.ab.	34153
56	54 or 55	53509
57	review.pt.	2398100
58	56 and 57	26635
59	letter.pt.	1054905
60	editorial.pt.	594275
61	animal/	1399005
62	human/	19123958
63	61 not (61 and 62)	1025168
64	or/59-60,63	2657877
65	38 or 47 or 53 or 58	377222
66	65 not 64	367018
67	1 and 32	7700
68	31 or 33 or 34 or 65	4581908
69	67 and 68	2278
70	limit 69 to human	2159
71	limit 70 to conference abstract status	490
72	70 not 71	1669

MEDLINE Search Strategy- Clinical Effectiveness of Vitamin D Testing

<b>Database(s): Ovid MEDLINE(R) ALL 1946 to January 18, 2019</b>		
Search Strategy:		
#	Searches	Results
1	exp mass screening/ or screening.mp. or testing.mp. or haemotologic test*.mp. or hemotologic test*.mp. or haemotological test*.mp. or hemotological test*.mp. or haemotology test*.mp. or hemotology test*.mp.	1085310
2	Randomized Controlled Trials as Topic/	120603
3	randomized controlled trial/	475004
4	Random Allocation/	97330
5	Double Blind Method/	149175
6	Single Blind Method/	26156
7	clinical trial/	514246
8	clinical trial, phase i.pt.	18582
9	clinical trial, phase ii.pt.	29985
10	clinical trial, phase iii.pt.	14550
11	clinical trial, phase iv.pt.	1642
12	controlled clinical trial.pt.	92881
13	randomized controlled trial.pt.	475004
14	multicenter study.pt.	244189
15	clinical trial.pt.	514246
16	exp Clinical Trials as topic/	321032
17	or/2-16	1272839
18	(clinical adj trial\$.tw.	324113
19	((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.	161257
20	PLACEBOS/	34199
21	placebo\$.tw.	201220
22	randomly allocated.tw.	25565
23	(allocated adj2 random\$.tw.	28680



24	or/18-23	577017
25	17 or 24	1508653
26	case report.tw.	282502
27	letter/	1013404
28	historical article/	349695
29	or/26-28	1630943
30	25 not 29	1474498
31	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfalcidol or calcitriol or colecalciferol).tw. or exp vitamin D/	81001
32	exp Cohort Studies/ and cohort.ti,ab.	257643
33	research subjects/ or exp clinical trials as topic/ or (research or trial? or study or studies or pilot or program\$ or longitudinal or prospective or retrospective).ti. or observational study as Topic/	2572122
34	(Meta-Analysis as Topic/ or meta analy\$.tw. or metaanaly\$.tw. or Meta-Analysis/ or (systematic adj (review\$1 or overview\$1)).tw. or exp Review Literature as Topic/ or cochrane.ab. or embase.ab. or (psychlit or psyclit).ab. or (psychinfo or psycinfo).ab. or (cinahl or cinhal).ab. or science citation index.ab. or bids.ab. or cancerlit.ab. or reference list\$.ab. or bibliograph\$.ab. or hand-search\$.ab. or relevant journals.ab. or manual search\$.ab. or ((selection criteria or data extraction).ab. and review/)) not (comment/ or letter/ or editorial/)	289323
35	1 and 31	2884
36	30 or 32 or 33 or 34	3739182
37	35 and 36	756
38	limit 37 to humans	621

CRD Search Strategy: Clinical Effectiveness of Vitamin D Testing

<b>CRD</b>
Results for: (vitamin D or cholecalciferol or ergocalciferol or calciferol or vitamin D2 or vitamin D3 or hydroxyvitamin D or vitamin-d or vitamin-d2 or vitamin-d3 or 25 hydroxyvitamin D or 25 hydroxyvitamin D2 or 25 hydroxyvitamin D3 or 25-hydroxyvitamin D or 25-hydroxy-vitamin D or 25-hydroxy-vitamin D2 or 25-hydroxy-vitamin D3 or 25OHD or 25-OH-vitamin D or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfalcidol or calcitriol or colecalciferol)
398 hits (385 after export)

Central Search Strategy: Clinical Effectiveness of Vitamin D Testing

<b>Central</b>
("vitamin D" OR cholecalciferol OR ergocalciferol OR calciferol OR "vitamin D2" OR "vitamin D3" OR "hydroxyvitamin D" OR vitamin-d OR vitamin-d2 OR vitamin-d3 OR "25 hydroxyvitamin D" OR "25 hydroxyvitamin D2" OR "25 hydroxyvitamin D3" OR "25-hydroxyvitamin D" OR "25-hydroxy-vitamin D" OR "25-hydroxy-vitamin D2" OR "25-hydroxy-vitamin D3" OR 25OHD OR "25-OH-vitamin D" OR "25-OHD" OR calcidiol OR calcifediol OR dihydrotacysterol OR alfalcidol OR calcitriol OR colecalciferol):ti,ab OR [mh "vitamin D"]
[mh "mass screening"] OR screening:ti,ab,kw OR testing:ti,ab,kw OR "haemotologic test*":ti,ab,kw OR "hemotologic test*":ti,ab,kw OR "haemotological test*":ti,ab,kw OR "hemotological test*":ti,ab,kw OR "haematology test*":ti,ab,kw OR "hematology test*":ti,ab,kw
#1 AND #2
Hits: 451

Epistemonikos Search Strategy: Clinical Effectiveness of Vitamin D Testing

<b>Epi</b>
(title:(title:(vitamin D) OR abstract:(vitamin D)) OR (title:(cholecalciferol) OR abstract:(cholecalciferol)) OR (title:(ergocalciferol) OR abstract:(ergocalciferol)) OR (title:(calciferol) OR abstract:(calciferol)) OR (title:(vitamin D2) OR abstract:(vitamin D2)) OR (title:(vitamin D3) OR abstract:(vitamin D3)) OR (title:(hydroxyvitamin D) OR abstract:(hydroxyvitamin D)) OR (title:(vitamin-d) OR abstract:(vitamin-d)) OR (title:(vitamin-d2) OR abstract:(vitamin-d2)) OR (title:(vitamin-d3) OR abstract:(vitamin-d3)) OR (title:(25 hydroxyvitamin D) OR abstract:(25 hydroxyvitamin D)) OR (title:(25 hydroxyvitamin D2) OR abstract:(25 hydroxyvitamin D2)) OR (title:(25 hydroxyvitamin D3) OR abstract:(25 hydroxyvitamin D3)) OR (title:(25-hydroxyvitamin D) OR abstract:(25-hydroxyvitamin D)) OR (title:(25-hydroxy-vitamin D) OR abstract:(25-hydroxy-vitamin D)) OR (title:(25-hydroxy-vitamin D2) OR abstract:(25-hydroxy-vitamin D2)) OR (title:(25-hydroxy-vitamin D3) OR abstract:(25-hydroxy-vitamin D3)) OR (title:(25OHD) OR abstract:(25OHD)) OR (title:(25-OH-vitamin D) OR abstract:(25-OH-vitamin D)) OR (title:(25-OHD) OR abstract:(25-OHD)) OR (title:(calcidiol) OR abstract:(calcidiol)) OR (title:(calcifediol) OR abstract:(calcifediol)) OR (title:(dihydrotacysterol) OR abstract:(dihydrotacysterol)) OR (title:(alfalcidol) OR abstract:(alfalcidol)) OR (title:(calcitriol) OR abstract:(calcitriol)) OR (title:(colecalciferol) OR abstract:(colecalciferol))) OR abstract:(title:(vitamin D) OR abstract:(vitamin D)) OR (title:(cholecalciferol) OR abstract:(cholecalciferol)) OR (title:(ergocalciferol) OR abstract:(ergocalciferol)) OR (title:(calciferol) OR abstract:(calciferol)) OR (title:(vitamin D2) OR abstract:(vitamin D2)) OR (title:(vitamin D3) OR abstract:(vitamin D3)) OR (title:(hydroxyvitamin D) OR

abstract:(hydroxyvitamin D)) OR (title:(vitamin-d) OR abstract:(vitamin-d)) OR (title:(vitamin-d2) OR abstract:(vitamin-d2)) OR (title:(vitamin-d3) OR abstract:(vitamin-d3)) OR (title:(25 hydroxyvitamin D) OR abstract:(25 hydroxyvitamin D)) OR (title:(25 hydroxyvitamin D2) OR abstract:(25 hydroxyvitamin D2)) OR (title:(25 hydroxyvitamin D3) OR abstract:(25 hydroxyvitamin D3)) OR (title:(25-hydroxyvitamin D) OR abstract:(25-hydroxyvitamin D)) OR (title:(25-hydroxy-vitamin D) OR abstract:(25-hydroxy-vitamin D)) OR (title:(25-hydroxy-vitamin D2) OR abstract:(25-hydroxy-vitamin D2)) OR (title:(25-hydroxy-vitamin D3) OR abstract:(25-hydroxy-vitamin D3)) OR (title:(25OHD) OR abstract:(25OHD)) OR (title:(25-OH-vitamin D) OR abstract:(25-OH-vitamin D)) OR (title:(25-OHD) OR abstract:(25-OHD)) OR (title:(calcidiol) OR abstract:(calcidiol)) OR (title:(calcifediol) OR abstract:(calcifediol)) OR (title:(dihyrotacysterol) OR abstract:(dihyrotacysterol)) OR (title:(alfacalcidol) OR abstract:(alfacalcidol)) OR (title:(calcitriol) OR abstract:(calcitriol)) OR (title:(colecalfiferol) OR abstract:(colecalfiferol))))

1515 hits

## Appendix 2. Keyword Search Strings - Economics of Vitamin D Testing

EMBASE Search: Economic Studies of Vitamin D Testing

Database(s): Embase 1974 to 2019 January 04		
Search Strategy:		
#	Searches	Results
1	(cost or costs).tw.	641415
2	exp screening/ or screening.mp. or testing.mp. or haemotologic test*.mp. or hemotologic test*.mp. or haemotological test*.mp. or hemotological test*.mp. or haemotology test*.mp. or hemotology test*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1622119
3	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or colecalciferol).tw. or exp vitamin D/	143542
4	1 and 2 and 3	390

MEDLINE search: Economic Studies of Vitamin D Testing

Database(s): Ovid MEDLINE(R) ALL 1946 to January 04, 2019		
Search Strategy:		
#	Searches	Results
1	(cost: or cost benefit analysis: or health care costs).mp.	629336
2	exp mass screening/ or screening.mp. or testing.mp. or haemotologic test*.mp. or hemotologic test*.mp. or haemotological test*.mp. or hemotological test*.mp. or haemotology test*.mp. or hemotology test*.mp.	1081735
3	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or colecalciferol).tw. or exp	80342

	vitamin D/	
4	1 and 2 and 3	173

#### CRD Search Strategy: Economic Studies of Vitamin D Testing

CRD
Results for: (vitamin D or cholecalciferol or ergocalciferol or calciferol or vitamin D2 or vitamin D3 or hydroxyvitamin D or vitamin-d or vitamin-d2 or vitamin-d3 or 25 hydroxyvitamin D or 25 hydroxyvitamin D2 or 25 hydroxyvitamin D3 or 25-hydroxyvitamin D or 25-hydroxy-vitamin D or 25-hydroxy-vitamin D2 or 25-hydroxy-vitamin D3 or 25OHD or 25-OH-vitamin D or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or colecalciferol)
398 hits (385 after export)

#### Appendix 3. Keyword Search Strings - Clinical Effectiveness of Vitamin D Supplementation

Database(s): Ovid MEDLINE(R) ALL 1946 to January 15, 2019		
Search Strategy:		
#	Searches	Results
1	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or colecalciferol).tw. or exp vitamin D/	80987
2	(Meta-Analysis as Topic/ or meta analy\$.tw. or metaanaly\$.tw. or Meta-Analysis/ or (systematic adj (review\$1 or overview\$1)).tw. or exp Review Literature as Topic/ or cochrane.ab. or embase.ab. or (psychlit or psychlit).ab. or (psychinfo or psychinfo).ab. or (cinahl or cinhal).ab. or science citation index.ab. or bids.ab. or cancerlit.ab. or reference list\$.ab. or bibliograph\$.ab. or hand-search\$.ab. or relevant journals.ab. or manual search\$.ab. or ((selection criteria or data extraction).ab. and review/)) not (comment/ or letter/ or editorial/)	289419
3	1 and 2	2074
4	limit 3 to (humans and yr="2000 -Current")	1671

Database(s): Embase 1974 to 2019 January 15		
Search Strategy:		
#	Searches	Results
1	("vitamin D" or cholecalciferol or ergocalciferol or calciferol or "vitamin D2" or "vitamin D3" or "hydroxyvitamin D" or vitamin-d or vitamin-d2 or vitamin-d3 or "25 hydroxyvitamin D" or "25 hydroxyvitamin D2" or "25 hydroxyvitamin D3" or "25-hydroxyvitamin D" or "25-hydroxy-vitamin D" or "25-hydroxy-vitamin D2" or "25-hydroxy-vitamin D3" or 25OHD or "25-OH-vitamin D" or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfacalcidol or calcitriol or coledcalciferol).tw. or exp vitamin D/	144407
2	exp Meta Analysis/	156319
3	((meta adj analy\$) or metaanalys\$).tw.	184897
4	(systematic adj (review\$1 or overview\$1)).tw.	165962
5	or/2-4	316973
6	cancerlit.ab.	725
7	cochrane.ab.	87178
8	embase.ab.	91275
9	(psychlit or psyclit).ab.	992
10	(psychinfo or psycinfo).ab.	24262
11	(cinahl or cinhal).ab.	26703
12	science citation index.ab.	3343
13	bids.ab.	612
14	or/6-13	142820
15	reference lists.ab.	17507
16	bibliograph\$.ab.	20716
17	hand-search\$.ab.	7444
18	manual search\$.ab.	4695
19	relevant journals.ab.	1312
20	or/15-19	46527
21	data extraction.ab.	21482
22	selection criteria.ab.	34151
23	21 or 22	53501
24	review.pt.	2396615
25	23 and 24	26637
26	letter.pt.	1054048
27	editorial.pt.	593677
28	animal/	1397915
29	human/	1911171 8
30	28 not (28 and 29)	1024410
31	or/26-27,30	2655670
32	5 or 14 or 20 or 25	376853
33	32 not 31	366672
34	1 and 33	3653
35	limit 34 to (human and yr="2000 -Current")	3445
36	limit 35 to conference abstract status	502
37	35 not 36	2943

<b>CRD</b>	
Results for: (vitamin D or cholecalciferol or ergocalciferol or calciferol or vitamin D2 or vitamin D3 or hydroxyvitamin D or vitamin-d or vitamin-d2 or vitamin-d3 or 25 hydroxyvitamin D or 25 hydroxyvitamin D2 or 25 hydroxyvitamin D3 or 25-hydroxyvitamin D or 25-hydroxy-vitamin D or 25-hydroxy-vitamin D2 or 25-hydroxy-vitamin D3 or 25OHD or 25-OH-vitamin D or 25-OHD or calcidiol or calcifediol or dihydrotacysterol or alfalcidol or calcitriol or colecalciferol)	398 hits

<b>Epistemonikos</b>	
(title:(title:(vitamin D) OR abstract:(vitamin D)) OR (title:(cholecalciferol) OR abstract:(cholecalciferol)) OR (title:(ergocalciferol) OR abstract:(ergocalciferol)) OR (title:(calciferol) OR abstract:(calciferol)) OR (title:(vitamin D2) OR abstract:(vitamin D2)) OR (title:(vitamin D3) OR abstract:(vitamin D3)) OR (title:(hydroxyvitamin D) OR abstract:(hydroxyvitamin D)) OR (title:(vitamin-d) OR abstract:(vitamin-d)) OR (title:(vitamin-d2) OR abstract:(vitamin-d2)) OR (title:(vitamin-d3) OR abstract:(vitamin-d3)) OR (title:(25 hydroxyvitamin D) OR abstract:(25 hydroxyvitamin D)) OR (title:(25 hydroxyvitamin D2) OR abstract:(25 hydroxyvitamin D2)) OR (title:(25 hydroxyvitamin D3) OR abstract:(25 hydroxyvitamin D3)) OR (title:(25-hydroxyvitamin D) OR abstract:(25-hydroxyvitamin D)) OR (title:(25-hydroxy-vitamin D) OR abstract:(25-hydroxy-vitamin D)) OR (title:(25-hydroxy-vitamin D2) OR abstract:(25-hydroxy-vitamin D2)) OR (title:(25-hydroxy-vitamin D3) OR abstract:(25-hydroxy-vitamin D3)) OR (title:(25OHD) OR abstract:(25OHD)) OR (title:(25-OH-vitamin D) OR abstract:(25-OH-vitamin D)) OR (title:(25-OHD) OR abstract:(25-OHD)) OR (title:(calcidiol) OR abstract:(calcidiol)) OR (title:(calcifediol) OR abstract:(calcifediol)) OR (title:(dihydrotacysterol) OR abstract:(dihydrotacysterol)) OR (title:(alfalcidol) OR abstract:(alfalcidol)) OR (title:(calcitriol) OR abstract:(calcitriol)) OR (title:(colecalciferol) OR abstract:(colecalciferol))) OR abstract:(title:(vitamin D) OR abstract:(vitamin D)) OR (title:(cholecalciferol) OR abstract:(cholecalciferol)) OR (title:(ergocalciferol) OR abstract:(ergocalciferol)) OR (title:(calciferol) OR abstract:(calciferol)) OR (title:(vitamin D2) OR abstract:(vitamin D2)) OR (title:(vitamin D3) OR abstract:(vitamin D3)) OR (title:(hydroxyvitamin D) OR abstract:(hydroxyvitamin D)) OR (title:(vitamin-d) OR abstract:(vitamin-d)) OR (title:(vitamin-d2) OR abstract:(vitamin-d2)) OR (title:(vitamin-d3) OR abstract:(vitamin-d3)) OR (title:(25 hydroxyvitamin D) OR abstract:(25 hydroxyvitamin D)) OR (title:(25 hydroxyvitamin D2) OR abstract:(25 hydroxyvitamin D2)) OR (title:(25 hydroxyvitamin D3) OR abstract:(25 hydroxyvitamin D3)) OR (title:(25-hydroxyvitamin D) OR abstract:(25-hydroxyvitamin D)) OR (title:(25-hydroxy-vitamin D) OR abstract:(25-hydroxy-vitamin D)) OR (title:(25-hydroxy-vitamin D2) OR abstract:(25-hydroxy-vitamin D2)) OR (title:(25-hydroxy-vitamin D3) OR abstract:(25-hydroxy-vitamin D3)) OR (title:(25OHD) OR abstract:(25OHD)) OR (title:(25-OH-vitamin D) OR abstract:(25-OH-vitamin D)) OR (title:(25-OHD) OR abstract:(25-OHD)) OR (title:(calcidiol) OR abstract:(calcidiol)) OR (title:(calcifediol) OR abstract:(calcifediol)) OR (title:(dihydrotacysterol) OR abstract:(dihydrotacysterol)) OR (title:(alfalcidol) OR abstract:(alfalcidol)) OR (title:(calcitriol) OR abstract:(calcitriol)) OR (title:(colecalciferol) OR abstract:(colecalciferol))))))	
SRs	1,484
BSs	29
All	4,277

#### Appendix 4. Characteristics of Clinical Studies of Vitamin D Testing

Main author	Year(s)	Title	Countries (if reported)	Group at high risk of severe vitamin D deficiency defined by FCN	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis
CADTH <sup>73</sup>	2014	Vitamin D Testing for Northern Populations: Clinical and Cost-Effectiveness and Guidelines	n/a	n/a (any)		SR	1 HTA, 0 SRs, 0 meta-analyses, 0 RCTs, 0 non-randomized studies, 0 economic evaluations, 0 evidence-based guidelines	0
CADTH <sup>74</sup>	2015	Vitamin D testing in the general population: clinical and cost-effectiveness and guidelines	n/a	n/a (any)		SR	Two SRs, 1 non-randomized study, one economic evaluation, and two evidence-based guidelines	0 (study design in the one non-randomized study was not eligible for our report)
LeBlanc <sup>72</sup>	2015	Screening for vitamin D deficiency: a systematic review for the U.S. Preventive Services Task Force.	n/a	n/a (any adults)		SR	0 randomised trials on vitamin D screening versus no screening on clinical outcomes	0

\*CADTH= Canadian Agency for Drugs and Technologies in Health. FCN= Federal Commission for Nutrition. HTA= health technology assessment. n/a=not applicable.

RCT= randomised controlled trial. SR= systematic review



## Appendix 5. Characteristics of Economic Analyses of Vitamin D Testing

Authors	Year	Title	Country	FCN risk group	Type of study	Intervention	Comparator	Modelling approach	Time horizon	Population
YHEC for NICE <sup>24</sup>	2014	An Economic Evaluation of Interventions to Improve the Uptake of Vitamin D Supplements in England and Wales	United Kingdom	Analysis 1: Older adults. Analysis 2: People with darker skin	Costing analysis	Testing the whole population for vitamin D deficiency and providing vitamin D supplementation only to those who are deficient	Vitamin D supplementation without prior testing	N/A	Not specified	Analysis 1: Older people aged 65 and over; Analysis 2: People with darker skin.
Lee ,Weber, Colton-Emeric <sup>75</sup>	2012	Cost-effectiveness analysis of screening for vitamin D insufficiency to prevent falls and fractures among community-dwelling older adults	USA	Older adults	Cost effectiveness analysis	Population screening for vitamin D insufficiency	No vitamin D screening or supplementation	Markov decision model, Treeage software	3 years	Analysis 1: community dwelling females aged 65-80 years. Analysis 2: community dwelling males aged 65-80 years.

Authors	Year	Title	Country	FCN risk group	Type of study	Intervention	Comparator	Modelling approach	Time horizon	Population
Zarca, Durand-Zaleski, et al. 76	2014	Cost-effectiveness analysis of hip fracture prevention with vitamin D supplementation: a Markov micro-simulation model applied to the French population over 65 years old without previous hip fracture.	France	Older adults	Cost effectiveness analysis	Analysis 1: Population screening for vitamin D insufficiency followed by treatment based on the vitamin D serum level. Analysis 2: Supplementation with a serum level check 3 months after initiation and subsequent treatment adaptation.	Analysis 1: no treatment. Analysis 2: Population screening for vitamin D insufficiency followed by treatment based on the vitamin D serum level.	Markov micro-simulation model, R statistical software	Lifetime	Adults with starting age of 65 years without previous hip fracture

KEY: \*FCN= Swiss Federal Commission for Nutrition. YHEC= York Health Economics Consortium. NICE= National Institute for Care and Health Excellence. n/a= not applicable

## Appendix 6. Results of Economic Analyses of Vitamin D Testing

Author	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention effect per person	Mean comparator effect per person	ICER	Currency	Annual discount rate (costs)	Annual discount rate (outcomes)	Threshold	Sensitivity analysis
YHEC for NICE <sup>24</sup>	2014	Analysis 1: 52.09. Analysis 2: 30.87	Analysis 1: 49.33. Analysis 2: 20.69.	n/a	n/a	N/A	GBP, year 2012	0%	0%	n/a	One-way sensitivity analyses were undertaken for the population of older people aged 65 and over, finding results were sensitive to prevalence of vitamin D deficiency, the cost of the test and the cost of the supplement
Lee, Weber, Colon-Emeric <sup>75</sup>	2012	Not reported*	Not reported*	Not reported*	Not reported*	Analysis 1: \$16,117 per QALY gained. Analysis 2: \$13,182 per QALY gained	USD, year 2011	3%	3%	\$50,000 per QALY	Analysis 1: PSA indicated population screening most cost-effective strategy in 52.8% of simulations, vitamin D supplementation without prior vitamin D testing cost-effective in 36.3% of simulations. Analysis 2: PSA indicated population screening most cost-effective strategy in 54.3% of simulations, vitamin D supplementation without prior vitamin D testing cost-effective in 38.2% of simulations

Author	Year	Mean intervention costs per person	Mean comparator costs per person	Mean intervention effect per person	Mean comparator effect per person	ICER	Currency	Annual discount rate (costs)	Annual discount rate (outcomes)	Threshold	Sensitivity analysis
Zarca, Du-rand-Zaleski, et al <sup>76</sup>	2014	Analysis 1: €709.21. Analysis 2: €684.63	Analysis 1: €684.63. Analysis 2: €606.89	Analysis 1: 11.148 QALYs. Analysis 2: 11.143 QALYs	Analysis 1: 11.143 QALYs. Analysis 2: 11.128 QALYs.	Analysis 1: €9,104 per QALY gained. Analysis 2: €5,219 per QALY gained.	Euros, year 2012	3%	3%	€20,000 per QALY	Analysis 1: For willingness-to-pay of over €6,000 per QALY, "Population screening for vitamin D insufficiency followed by treatment" strategy had the greatest probability of being cost-effective

\*The authors of this study neglected to report absolute costs and QALYs for each treatment strategy.

KEY: \*\*ICER=incremental cost-effectiveness ratio. n/a= not applicable. QALY= quality adjusted life year. GBP= Great British pounds. USD= USA dollars.

## Appendix 7. Characteristics of the Umbrella and Systematic Reviews of Vitamin D Supplementation (n=21)

Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
<b>PEOPLE WITH BONE DISORDERS</b>								
Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	Predominantly United Kingdom	High risk of fracture	Umbrella review	24 MAs	2 SRs (first SR comprising a total of 2745 participants; second SR comprising a total of 109 participants)	1a
Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	Not stated	High risk of fracture	Umbrella review	24 MAs	1 SR, 1 trial comprising a total of 213 participants	1b
Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	United Kingdom	High risk of fracture	Umbrella review	24 MAs	1 SR, 3 trials comprising a total of 2820 participants	1c
Egan <sup>86</sup>	2008	Factors associated with a second hip fracture: a systematic review	United Kingdom	Individuals who have previously fractured a hip	Systematic review	4 RCTs	1 RCT; 76 participants in relevant groups	2
Parikh <sup>87</sup>	2009	Pharmacological Management of Osteoporosis in Nursing Home Populations: A Systematic Review	France, Switzerland	Female nursing home residents; at least 79 years of age (thus likely to have osteoporosis).	Systematic review	8 RCTs	3 RCTs	3
Qaseem <sup>85</sup>	2017	Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians	Not stated	Low bone density or osteoporosis	Systematic review	Not stated	68 studies	4
<b>OLDER ADULTS</b>								
Bolland subgroup <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	Large proportion of trials from Europe, Australia, USA (may also be some from LMICs)	Mostly (not exclusively) adults aged 65 and over	Umbrella/systematic review	42 RCTs on total fracture	19 RCTs included in subgroup meta-analysis of daily vitamin D supplementation	5a
Bolland subgroup <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	Large proportion from Europe, Australia, USA (may also be some from LMICs)	Mostly (not exclusively) adults aged 65 and over	Umbrella/systematic review	37 RCTs on falls	18 RCTs included in subgroup meta-analysis of daily vitamin D supplementation	5b

Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
Bolland sub-group <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	Large proportion from Europe, Australia, USA (may also be some from LMICs)	Mostly (not exclusively) adults aged 65 and over	Umbrella/systematic review	41 RCTs on BMD	18 RCTs included in subgroup meta-analysis of daily vitamin D supplementation	5c
Bjelakovic <sup>98</sup>	2014	Vitamin D supplementation for prevention of mortality in adults	USA, UK, Finland	Postmenopausal women and older men	Cochrane review	159 trials	4 randomised trials; 44,492 participants	6
Husebo <sup>99</sup>	2016	Identifying and Managing Pain in People with Alzheimer's Disease and Other Types of Dementia: A Systematic Review	Finland	Advanced dementia patients	Systematic review	12 studies	1 RCT; 202 participants	7
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	4 SRs (17 RCTs)	8a
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	3 SRs (9 RCTs)	8b
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	1 SR (15 RCTs, 28,271 participants)	8c
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	1 SR (10 RCTs, 49,853 participants)	8d
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	1 SR (6 RCTs, 46,794 participants)	8e
Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	Mostly USA, Canada, UK, Sweden, Netherlands	≥65 years old	Umbrella review	28 SRs	1 SR (18 RCTs, 22,854 participants)	8f
Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	Europe and USA	≥60 years old	Umbrella review	24 SRs	3 SRs (21 RCTs, 12,821 participants)	9a
Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	Europe and USA	≥60 years old	Umbrella review	24 SRs	4 SRs (34 RCTs)	9b
Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	Europe and USA	≥60 years old	Umbrella review	24 SRs	2 SRs (22 RCTs, 223,048 participants)	9c
Stubbs <sup>93</sup>	2015	What works to prevent falls in older adults dwelling in long term care facilities and hospitals? An umbrella review of meta-analyses of randomised controlled trials.	Not stated	≥60 years old in care facilities	Umbrella review	26 SRs	5 SRs (30 RCTs)	10a
Stubbs <sup>88</sup>	2015	What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials	Not stated	≥60 years old	Umbrella review	16 SRs	4 SRs (32 RCTs)	11a

Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
Stubbs <sup>88</sup>	2015	What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials	Not stated	≥65 years old	Umbrella review	16 SRs	5 SRs (36 RCTs)	11b
Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	Switzerland, New Zealand, UK	≥65 years old, community dwelling	Umbrella review	17 SRs	3 RCT (752 participants)	12a
Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	Germany	≥65 years old, community dwelling	Umbrella review	17 SRs	1 RCTs (148 women)	12b
Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	Switzerland	≥65 years old, community dwelling	Umbrella review	17 SRs	1 RCTs (2566 participants)	12c
Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	UK	≥65 years old, community dwelling	Umbrella review	17 SRs	2 RCTs (3,980 participants)	12d
De Spiegleer <sup>95</sup>	2018	Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses	Europe, USA, Australia, Brazil, Canada and Japan	≥65 years old	Umbrella review	7 SRs	2 SRs (3,049 participants)	13a
De Spiegleer <sup>95</sup>	2018	Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses	Europe, USA, Australia, Brazil, Canada and Japan	≥65 years old	Umbrella review	7 SRs	2 SRs (1,223 participants)	13b
Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	Not stated	> 60 years old women	Umbrella review	71 SRs	1 SR (5 RCTs, 9,138 participants)	14a
Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	Not stated	> 60 years old women	Umbrella review	71 SRs	2 SRs (13 RCTs, 44,065 participants)	14b
Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	Not stated	> 60 years old women	Umbrella review	71 SRs	2 SRs (7 RCTs, 96,121 participants)	14c
Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	Not stated	> 60 years old women	Umbrella review	71 SRs	3 SRs (18 RCTs, 110,010 participants)	14d
Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	Not stated	> 60 years old	Umbrella review	87 MAs	10 RCTs (34,144 participants)	15a
Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	Not stated	> 60 years old	Umbrella review	87 MAs	10 RCTs (25,016 participants)	15b
Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	UK, Switzerland, New Zealand, Japan, Germany, USA, Australia	> 60 years old	Umbrella review	87 MAs	3 RCTs (314 participants)	15c
<b>OBESE INDIVIDUALS</b>								

Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
Bassatne <sup>103</sup>	2019	Vitamin D supplementation in obesity and during weight loss: A review of randomized controlled trials.	Norway	Mean BMI of participants $\geq 30$ kg/m <sup>2</sup> in at least one arm) without weight loss	Systematic review	26	1 RCT	16
<b>PREGNANT WOMEN</b>								
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran, India	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 4 trials, 499 women,	17a
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	United Kingdom	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 1 trial, 126 women,	17b
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran, France, New Zealand, United Kingdom, Bangladesh, India	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 7 trials, 1640 women,	17c
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran, India	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 4 trials, 446 women,	17d



Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran, India	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 4 trials, 1174 women,	17e
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 1 trial, 54 women,	17f
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Brazil, Iran	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 2 trials, 110 women,	17g
Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	Iran, Brazil	Pregnant women	Umbrella review/systematic review	25 SRs	1 SR, 5 trials, 942 women,	17h
Harvey <sup>106</sup>	2014	Vitamin D supplementation in pregnancy: A systematic review	United Kingdom	Pregnant women	Systematic review	76 studies	1 trial	18
Cranney <sup>33</sup>	2007	Effectiveness and safety of vitamin D in relation to bone health		Women of reproductive age	Systematic review	167	0 trials	19a

Main author	Year(s)	Title	Countries (if reported)*	FCN at risk group (sub-group)	Type of study	Number of studies in review	Number of studies relevant for our analysis	Code for analysis (to match with results in appendix 8)
Cranney <sup>33</sup>	2007	Effectiveness and safety of vitamin D in relation to bone health	n/a	Women of reproductive age	Systematic review	167	0 trials	19b
<b>ATHLETES</b>								
Farrokhyar <sup>108</sup>	2017	Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials	n/a		Systematic review	13 RCTs (532 athletes)	0	20a
Farrokhyar <sup>108</sup>	2017	Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials	Not stated		Systematic review	13 RCTs (532 athletes)	7	20b
Chiang <sup>109</sup>	2017	Effects of Vitamin D Supplementation on Muscle Strength in Athletes: A Systematic Review	United Kingdom, USA	healthy, athletic participants aged 18-45 years	Systematic review	6 trials (5 RCTs, 1 non-randomised controlled trial)	4	21a
Chiang <sup>109</sup>	2017	Effects of Vitamin D Supplementation on Muscle Strength in Athletes: A Systematic Review	USA	healthy, athletic participants aged 18-45 years	Systematic review	6 trials (5 RCTs, 1 non-randomised controlled trial)	2	21b

Key: MA=meta-analysis. RCT=randomized controlled trial. SR=systematic review. UR=umbrella review. USA=United States of America. UK=United Kingdom. FCN= Swiss Federal Commission for Nutrition. n/a=not applicable.

\*Refers to the countries in which the underlying trials were conducted. \*\*Some studies appear more than once in table as they address multiple outcomes/vitamin D modalities for a particular risk group

## Appendix 8. Results of the Umbrella and Systematic Reviews of Vitamin D Supplementation (n=21)

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
<b>PERSONS WITH BONE DISORDERS</b>													
1a	Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	1	High risk of fracture	1966-2007	Not stated	Vitamin D	Placebo	Vertebral fracture	SR1: RR=3.97 (95% CI: 0.44, 35.45); SR2: RR=1.02 (95% CI: 0.44 to 2.32)	Both SRs reported that vitamin D did not affect risk of vertebral fracture	6
1b	Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	1	High risk of fracture	1966-2007	Not stated	Vitamin D	Placebo	Non-vertebral fracture	5% (n=5) of vitamin D group experienced non-vertebral fracture; 11% (n=12) of placebo group experienced non-vertebral fracture; RR was not statistically significant (and not numerically reported)	Based on 1 trial of 213 participants, vitamin D did not significantly affect risk of non-vertebral fracture	6
1c	Maclean <sup>81</sup>	2008	Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis	1	High risk of fracture	1966-2007	1 year to 5 years	Vitamin D	Placebo	Hip fracture	RR=1.08 (95% CI: 0.72 to 1.62)	Based on 3 trials, vitamin D did not significantly affect risk of hip fracture	6

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
2	Egan <sup>86</sup>	2008	Factors associated with a second hip fracture: a systematic review	1	Individuals who have previously fractured a hip	Inception-2006	12 months	Daily 800 IU Vitamin D3 plus 1g calcium	No treatment	Second fracture within 12 months of the first	8% (n=3) of vitamin D plus calcium group experienced second fracture; 14% (n=5) of placebo group experienced second fracture	Due to small sample size, unable to assess whether vitamin D plus calcium significantly reduces second fracture risk	5
3	Parikh <sup>87</sup>	2009	Pharmacological Management of Osteoporosis in Nursing Home Populations: A Systematic Review	1	Female nursing home residents; at least 79 years of age (thus likely to have osteoporosis).	1974-2006	1.5 to 2 years	800 IU vitamin D daily plus calcium	Placebo or no intervention	Bone mineral density	All 3 trials found vitamin D plus calcium was associated with higher BMD outcomes; however confidence intervals were not reported	The evidence base supported the use of vitamin D at a dose of 800IU or greater in NH populations for improving BMD	5
4	Qaseem <sup>85</sup>	2017	Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update From the American College of Physicians	1	Low bone density or osteoporosis	2005-2016	Not stated	Vitamin D	Various	Fracture	The overall effect of vitamin D monotherapy in reducing fracture risk is uncertain due to mixed findings across MAs/trials; evidence is of a moderate quality (GRADE assessment)	n/a	3
<b>OLDER ADULTS</b>													

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
5a	Bolland subgroup <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	2		Database search from 2015-2018 as an update to previously published meta-analyses	Estimated at 1-60 months	Subgroup receiving daily vitamin D supplementation	Untreated controls, placebo, or lower-dose vitamin D supplements	Total fracture	RR=0.97, (95% CI: 0.88 to 1.07)	Daily vitamin D supplementation does not appear to prevent total fracture in older adults.	6
5b	Bolland subgroup <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	2		Database search from 2015-2018 as an update to previously published meta-analyses	Estimated at 1-60 months	Subgroup receiving daily vitamin D supplementation	Untreated controls, placebo, or lower-dose vitamin D supplements	Falls	RR=0.92, (95% CI: 0.87 to 0.98)	Daily vitamin D supplementation resulted in a statistically significant reduction in falls in older adults.	6

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
5c	Bolland subgroup <sup>77</sup>	2018	Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis	2	Mostly (not exclusively) adults aged 65 and over	Database search from 2015-2018 as an update to previously published meta-analyses	Estimated at 1-60 months	Subgroup receiving daily vitamin D supplementation	Untreated controls, placebo, or lower-dose vitamin D supplements	Lumbar spine BMD	(Assumed) Weighted mean percentage difference=0.10%; 95% CI: -0.21% to 0.41%	Daily vitamin D supplementation does not appear to have a clinically meaningful effect on lumbar spine BMD.	6
6	Bjelakovic <sup>98</sup>	2014	Vitamin D supplementation for prevention of mortality in adults	2	Postmenopausal women and older men	Inception-2012	5 to 7 years	Vitamin D	Placebo or no intervention	Cancer mortality	RR=0.88 (95% CI: 0.78 to 0.98)	Vitamin D3 statistically significantly decreased cancer mortality; based on moderate quality evidence	11
7	Husebo <sup>99</sup>	2016	Identifying and Managing Pain in People with Alzheimer's Disease and Other Types of Dementia: A Systematic Review	2	Advanced dementia patients	1990-2015	6 months	Cholecalciferol	Placebo	Pain	p>0.10 for all pain measures	Pain scores not changed after vitamin D treatment	7

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
8a	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D only	Placebo or calcium only or no intervention	Falls	Kalyani 2010: RR=0.94 (95% CI 0.77 to 1.15); Bischoff-Ferrari 2009: RR=0.81 (95% CI 0.71 to 0.92); Cameron 2012: RR=0.99 (95% CI 0.90 to 1.08) but showed a significant rate ratio of 0.63 (95% CI 0.46 to 0.86); Neyens 2011: based on one RCT OR=0.82 (95% CI 0.59 to 1.12) and rate ratio of 0.73 (95% CI 0.57 to 0.95)	One SR reported significant effect of vitamin D therapy on falls. Two SRs reported effect on rate, and one reported non-significant effect on falls.	4

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
8b	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D & calcium	Placebo or no intervention	Falls	Kalyani 2010: RR= 0.83, 95% CI 0.75 to 0.92); Bischoff-Ferrari 2009: one study of the MA reported 19% non significant reduction in falls; Cameron 2012: RR=0.82 (95% CI 0.40 to 1.66 ) but reported a rate ratio of 0.38 (95% CI 0.20 to 0.71)	One SR reported significant effect of vitamin D plus calcium on falls. One reported non-significant effect on falls. One reported effect on rate of falls but not on risk of falls.	4
8c	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D only	Placebo or calcium or no intervention	Fractures (hip and others)	Avenell 2014: RR=1.12 (95% CI 0.98 to 1.29) for hip fracture and RR= 1.03 (95% CI 0.90 to 1.11) for any type of fracture	One SR reported that taking vitamin D only is unlikely to prevent fractures.	4
8d	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D & calcium	Placebo or no intervention	Fractures (hip and others)	Avenell 2014: hip fracture risk RR=0.84 (95% CI 0.74 to 0.96) and risk of any type of fracture RR=0.95 ( 95% CI 0.90 to 0.99)	Evidence from one SR showed that vitamin D taken with additional calcium supplements slightly reduces the likelihood of hip fractures and other types of fracture.	4
8e	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D & calcium	Placebo or no intervention	All-cause mortality	Avenell 2014: RR=0.94 (95% CI 0.87 to 1.02)	Mortality was not adversely affected by vitamin D plus Calcium	4



Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
8f	Poscia <sup>90</sup>	2017	Effectiveness of nutritional interventions addressed to elderly persons: umbrella systematic review with meta-analysis	2	≥65 years old	2000 to 2016	1 to 66 months	Vitamin D only	Placebo or calcium or no intervention	All-cause mortality	Avenell 2014: RR=0.99 (95% CI 0.94 to 1.03)	The SR reported insignificant results on mortality as an adverse effect of vitamin D supplementation	4
9a	Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	2	≥60 years old	2007 to 2012	3 to 36 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	Falls	Bischoff-Ferrari 2009: RR=0.81 (95% CI 0.71 to 0.92); Cameron (updated in 2012): RR=0.99 (95% CI 0.90 to 1.08) but showed a significant rate ratio of 0.63 (95% CI 0.46 to 0.86); Michael 2010: RR=0.83 (95% CI 0.77 to 0.89)	3 SRs reported that vitamin D reduces either the risk or rate of falls.	1

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
9b	Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	2	≥60 years old	2007 to 2012	1 to 84 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	Fractures	Bischoff-Ferrari 2009: RR=0.86 (95% CI 0.77 to 0.96) for non-vertebral fracture and RR=0.91 (95% CI: 0.78 to 1.05) for hip fracture ; Avenell 2009: RR=1.01 (95% CI 0.93 to 1.09) for total fracture, significant results only for vitamin D plus Calcium for hip fracture risk RR=0.84 (95% CI 0.73 to 0.96); Sawka 2009: RR=0.86 (95% CI 0.74 to 0.98) hip fracture ; Chung: total fracture vitamin D plus calcium RR=0.88 (95% CI 0.79 to 0.99) Vitamin D only RR=1.03 (95% CI 0.84 to 1.26)	Two SRs concluded that vitamin D was only beneficial when combined with calcium. In contrast, the other two SRs concluded that vitamin D alone was beneficial only in doses exceeding 482 IU per day.	1

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
9c	Scragg <sup>91</sup>	2012	Do we need to take calcium with vitamin D to prevent falls, fractures and death?	2	≥60 years old	2007 to 2012	Maximum 60 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	All-cause mortality	Avenell 2009: RR=0.94 (95% CI 0.89 to 0.99) vitamin D plus Ca, RR=1.01 (95% CI 0.95 to 1.06) for vitamin D alone; Rejnmark 2012: RR=0.93 (95% CI 0.88 to 0.99) for vitamin D with or without Ca, RR=0.92 (95% CI 0.85 to 1.00) for vitamin D plus Ca, RR=0.99 (95% CI 0.89 to 1.09) for vitamin D alone	Both SRs included found that combined vitamin D and calcium supplementation decreases all-cause mortality.	1

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
10a	Stubbs <sup>93</sup>	2015	What works to prevent falls in older adults dwelling in long term care facilities and hospitals? An umbrella review of meta-analyses of randomised controlled trials.	2	≥60 years old in care facilities	Inception to 2014	Not reported	Vitamin D with or without calcium	Placebo or calcium or no intervention	Falls	Gou 2013:OR=0.98 (95% CI 0.79 to 1.22);Cameron 2012: RR=0.99 (95% CI 0.90 to 1.08) but showed a significant rate ratio of 0.63 (95% CI 0.46 to 0.86);Kalyani 2010: RR=0.90 (95% CI 0.80 to 1.01); Murad 2011: OR 0.87 (95% CI 0.71 to 1.07); Bolland 2014: RR=0.96 (95% CI 0.88 to 1.05)	Only one out of five SRs demonstrated a significant reduction in the rate of falls. Of the remainder, one SR demonstrated a trend towards significance and two poolings from another SR demonstrated a non-significant reduction in the risk of falling from vitamin D supplementation with and without calcium. Given this, evidence does not support vitamin D supplementation to reduce falls in LTCF; based on evidence authors assessed to be moderate and high quality.	7
11a	Stubbs <sup>88</sup>	2015	What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials	2	≥60 years old	Inception to 2014	Not reported	Vitamin D & calcium	Placebo or no intervention	Falls	Bolland 2014: RR=0.93 (95% CI 0.85 to 1.02); Gou 2014: RR=0.78 (95% CI 0.63 to 0.98);Kalyani 2010: RR=0.83, 95% CI 0.75 to 0.92); Murad 2011: OR=0.83 (95% CI 0.72 to 0.93)	SRs concluded that vitamin D was beneficial when combined with calcium in older adults	7

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
11b	Stubbs <sup>88</sup>	2015	What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials	2	≥65 years old	Inception to 2014	Not reported	Vitamin D only	Placebo or no intervention	Falls	Bolland 2014: RR=0.96 (95% CI 0.88 to 1.04); Gou 2014: RR=1.02 (95% CI 0.80 to 1.28); Kalyani 2010: RR=0.83 (95% CI 0.75 to 0.92); Murad 2011: OR=0.97 (95% CI 0.84 to 1.11); Jackson 2007: RR=0.92 (95% CI 0.75 to 1.12)	Supplementation with Vitamin D alone appears to be statistically non-effective in 4 out of 5 SRs.	7
12a	Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	2	≥65 years old, community dwelling	2000 to 2007	1 to 6 months	Vitamin D only	Placebo or no intervention	Falls	RR=0.94 (95% CI 0.77 to 1.14)	The results of the SR indicated that supplementation with vitamin D does not significantly reduce the risk of falling in the community-dwelling elderly population	5
12b	Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	2	≥65 years old, community dwelling	2000 to 2007	12 months	Vitamin D & calcium	Placebo or no intervention	Fall-related injuries	RR=0.48 (95% CI, 0.12–1.84)	Supplementation with vitamin D does not significantly reduce the risk of fall-related injuries in the community-dwelling elderly women.	5
12c	Medical Advisory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Seniors	2	≥65 years old, community dwelling	2000 to 2007	36 months	Vitamin D & calcium	Placebo or calcium or no intervention	Falls	RR=0.89 (95% CI 0.74 to 1.07) for men and women; RR=0.83 (95% CI 0.73 to 0.95) for women only.	The evidence does not suggest a statistically significant reduction in falls in the study that included both men and women in their study population but for the women only study population the reduction in falls was significant.	5

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of re- view)	Duration of follow- up of in- cluded studies	Interven- tion(s)	Compar- ator(s)	Outcomes relevant to our analy- sis	Results*	Summary	AMSTAR score**
12d	Medical Ad- visory <sup>89</sup>	2008	Prevention of Falls and Fall Related Injuries in Community-Dwelling Sen- iors	2	≥65 years old, com- munity dwelling	2000 to 2007	1 to 36 months	Vitamin D & calcium	Placebo or cal- cium or no inter- vention	Fall-re- lated frac- ture	RR=0.77 (95% CI 0.49 to 1.21)	The evidence does not sug- gest a statistically significant reduction in fall-related inju- ries in women	5

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
13a	De Spiegeleer <sup>95</sup>	2018	Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses	2	≥65 years old	Inception to 2017	Not reported	Vitamin D with or without calcium	Placebo or no intervention	Muscle strength	Anagnostis 2015: Knee extension: SMD=0.05 (95% CI 0.11–0.20). (1) Global muscle strength: SMD=0.25 (95% CI 0.01–0.48). Institutionalised and hospitalised vs. community dwelling: SMD 0.45 vs. 0.05; p < 0.01 (2) Grip strength: SMD=0.01 (95% CI –0.06–0.07) (3) Lower limb muscle strength: SMD 0.19 (95% CI 0.05–0.34); Beaudart 2017: Both studies reported no difference between the exercise-only group and the group with combined exercise and vitamin D supplementation.	Only 1 out of the 2 included SRs found positive effect on muscle strength; but authors described there is sufficient evidence in favour (women).	5

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
13b	De Spiegeleer <sup>95</sup>	2018	Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses	2	≥65 years old	Inception to 2017	Not reported	Vitamin D with or without calcium	Placebo or no intervention	Physical (functional) performance	Anagnostis 2015:TUG: SMD= - 0.19 (95% CI - 0.35 to - 0.02); p = 0.03 Gait: an effect on gait was not found, although the studies that evaluated gait were of lower methodological quality and used low doses of vitamin D; Beudart 2017: Physical performance increased, for some of the physical performance outcomes, in 2/2 RCTs with no additional effect of vitamin D, except for TUG in 1/2 RCTs	Some evidence in favour of improved physical performance when supplementing with vitamin D. The effects are most pronounced when supplementing those with serum levels < 10 ng/ml. Recommended vitamin D supplementation to improve physical performance in older people, especially women, with low baseline serum levels.	5
14a	Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	2	> 60 years old women	Inception to 2010	1 to 5 years	Vitamin D only	Placebo or no intervention	Vertebral fracture	Avenell 2009: RR=0.90 (95% CI 0.42 to 1.92)	Compared with placebo or no treatment Vitamin D seems no more effective at reducing vertebral fractures in women and in men aged over 65 years (moderate-quality evidence).	6



Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
14b	Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	2	> 60 years old women	Inception to 2010	1 to 5 years	Vitamin D only	Placebo or no intervention	Non-vertebral fracture	Avenell 2009: hip fracture RR=1.15 (95% CI 0.99 to 1.33); Dipart 2010 : HR=1.09 (95% CI 0.92 to 1.29)	Compared with placebo or no treatment Vitamin D seems no more effective at reducing any non-vertebral fracture or hip fracture in postmenopausal women and in men aged over 65 years (moderate-quality evidence).	6
14c	Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	2	> 60 years old women	Inception to 2010	1 to 5 years	Vitamin D & calcium	Placebo or calcium or no intervention	Vertebral fracture	Avenell 2009: RR=0.91 (95% CI 0.75 to 1.11; Dipart 2010 : HR=0.85 (95% CI 0.66 to 1.11)	Compared with placebo or no treatment Calcium plus vitamin D may be no more effective at reducing the risk of vertebral fractures in postmenopausal women or in men aged over 65 years (low-quality evidence)	6
14d	Vestergaard <sup>94</sup>	2010	Fracture prevention in postmenopausal women	2	> 60 years old women	Inception to 2010	1 to 5 years	Vitamin D & calcium	Placebo or calcium or no intervention	Non-vertebral fracture	Avenell 2009: RR=0.95 (95% CI 0.90 to 1.00); Dipart 2010: hip fracture HR=0.84 (95% CI 0.70 to 1.01;); Bischoff-Ferrari 2009: RR= 0.77 ( 95% CI 0.68 to 0.87)	Compared with placebo or no treatment Calcium plus vitamin D may be more effective at reducing the risk of nonvertebral fractures in postmenopausal women or in men aged over 65 years (low-quality evidence).	6

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
15a	Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	2	> 60 years old	Inception to 2013	Maximum 48 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	Falls	OR=0.97 (95% CI 0.84 to 1.11)	11 SRs examined risk of falling, and differences existed in both the magnitude and the statistical significance of the effect but not in the direction of the effect. Finally, three meta-analyses examined rate of falls, and differences existed in the direction, magnitude, and statistical significance of the effect. The MA of non overlapping MAs reported non significant effect.	3
15b	Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	2	> 60 years old	Inception to 2013	Maximum 48 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	Fractures	RR=1.01 (95% CI: 0.93 to 1.09)	10 SRs reported conflicting results. The MA of non overlapping MAs reported non significant effect.	3
15c	Theodoratou <sup>92</sup>	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials	2	> 60 years old	Inception to 2013	3 to 24 months	Vitamin D with or without calcium	Placebo or calcium or no intervention	Physical performance (balance sway/lower extremity strength)	Balance sway SMD= -0.20 (95% CI -0.39 to -0.01); lower extremity strength: SMD=0.05 (95% CI -0.11 to 0.20)	Improved balance sway (significant effect) and lower extremity strength (non-significant effect) when supplementing with vitamin D.	3
<b>OBESE INDIVIDUALS</b>													
16	Bassatine <sup>103</sup>	2019	Vitamin D supplementation in obesity and during weight loss: A review of randomized controlled trials.	3	Mean BMI of participants $\geq 30$ kg/m <sup>2</sup> in at least one arm) without weight loss	2010-2018	12 months	Vitamin D3	Placebo	Bone mineral density	No significant differences were found between the three groups regarding change in BMD	There were no significant changes in BMD between nor within treatment arms. Furthermore, in the protocol of the one RCT included, BMD was not pre-specified in the trial protocol	4

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
<b>PREGNANT WOMEN</b>													
17a	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D monotherapy	placebo/no intervention	Pre-eclampsia	n/a	No trials were found evaluating effect of intervention in high-income setting	11
17b	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	3 months	Vitamin D monotherapy	placebo/no intervention	low birthweight (less than 2500 g)	(RR 0.53, 95% CI 0.23 to 1.21;	Only one trial from high-income country setting on effect of vitamin D monotherapy on low birthweight; which was published in 1980 and supplemented women of Asian origin only	11
17c	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	3 to 6 months	Vitamin D monotherapy	placebo/no intervention	preterm birth < 37 weeks	(RR 0.66, 95% CI 0.34 to 1.30;	Vitamin D supplementation may make little or no difference in the risk of having a preterm birth < 37 weeks (low-certainty evidence)	11
17d	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D monotherapy	placebo/no intervention	Maternal gestational diabetes	n/a	No trials were found evaluating effect of intervention in high-income setting	11

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
17e	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D and calcium	placebo/no intervention	pre-eclampsia	n/a	No trials were found evaluating effect of intervention in high-income setting	11
17f	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D and calcium	placebo/no intervention	maternal gestational diabetes	n/a	No trials were found evaluating effect of intervention in high-income setting	11
17g	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D and calcium	placebo/no intervention	low birth-weight (less than 2500 g)	n/a	No trials were found evaluating effect of intervention in high-income setting	11
17h	Browne (and De-Regil) <sup>104</sup>	2016 (with 2019 update of included SR presented)	Vitamin D supplementation for women during pregnancy	4	Pregnant women	Inception to 2018	n/a	Vitamin D and calcium	placebo/no intervention	preterm birth < 37 weeks	n/a	No trials were found evaluating effect of intervention in high-income setting	11

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
18	Harvey <sup>106</sup>	2014	Vitamin D supplementation in pregnancy: A systematic review	4	Pregnant women	Inception to 2012	circa 3 months	Vitamin D and calcium	no intervention	Offspring forearm bone mineral content	Mean bone mass outcome of 3.10 units in comparator group; 3.19 units in intervention group. No p value given	There was no significant difference in the bone mineral content (as assessed by photon absorptiometry) of the forearms of babies born to these women between the intervention and comparator groups. The study was assessed to have a high risk of bias	8
19a	Cranney <sup>33</sup>	2007	Effectiveness and safety of vitamin D in relation to bone health	4	Women of reproductive age	Inception-2006	n/a	Vitamin D	Control	Bone mineral density	n/a	No trials were found evaluating effect of intervention on BMD in any setting for pregnant women	7
19b	Cranney <sup>33</sup>	2007	Effectiveness and safety of vitamin D in relation to bone health	4	Women of reproductive age	Inception-2006	n/a	Vitamin D	Control	Fractures	n/a	No trials were found evaluating effect of intervention on fractures in any setting for pregnant women	7
<b>ATHLETES</b>													
20a	Farrokhvar <sup>108</sup>	2017	Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials	6		Inception-2016	n/a	Vitamin D supplement	Placebo or no intervention	Injury (stress fractures, or muscle and connective tissue injury)	n/a	No RCTs were found that formally assess the impact of vitamin D supplementation in preventing injury in athletes. However, one trial reported 16 muscle and connective tissue injuries over 24 weeks, and recorded that 77% of the injured athletes reported the injury after a decrease in their vitamin D level from baseline.	9

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
20b	Farrokhyar <sup>108</sup>	2017	Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials	6		Inception-2016	12 weeks	Vitamin D supplement	Placebo or no intervention	Physical performance	Hand grip strength (three trials) increased significantly (2.56 kg; 95% CI: 1.00–4.13) after 12 weeks' vitamin D supplementation of 2000–3800 IU. No significant differences were found in vertical jump height (0.92 cm; 95% CI:-0.55 to 2.44), one repetition maximum (1-RM) bench press (2.05; 95% CI:-5.5 to 9.6) or 10- to 30-m sprint (0.04 s; 95% CI:-0.04 to 0.12)	Physical performance did not significantly improve from vitamin D supplementation	9

Code for analysis (see appendix 7)	Main author	Year	Title	FCN at risk group	FCN at risk group (subgroup)	Methods (Time range of review)	Duration of follow-up of included studies	Intervention(s)	Comparator(s)	Outcomes relevant to our analysis	Results*	Summary	AMSTAR score**
21a	Chiang <sup>109</sup>	2017	Effects of Vitamin D Supplementation on Muscle Strength in Athletes: A Systematic Review	6	healthy, athletic participants aged 18-45 years	2010-2016	4 weeks to 6 months	Cholecalciferol	Placebo	Muscle strength	In 2 studies, strength outcome measures were significantly improved after supplementation (p<=0.05). In the other 2 studies administering vitamin D3, there were trends for improved muscle strength	Vitamin D3 was shown to have a positive impact on muscle strength.	3
21b	Chiang <sup>109</sup>	2017	Effects of Vitamin D Supplementation on Muscle Strength in Athletes: A Systematic Review	6	healthy, athletic participants aged 18-45 years	2010-2016	4 weeks to 6 months	Ergocalciferol	Placebo	Muscle strength	p>0.05 in each of the studies	Vitamin D2 was found to be ineffective at impacting muscle strength in both studies wherein it was administered.	3

Key: MA=meta-analysis, RCT=randomised controlled trial, SR=systematic review, UR=umbrella review, FCN= Swiss Federal Commission for Nutrition at high risk of severe vitamin D deficiency defined by FCN group 1 (persons with bone disorders), 2 (older adults), 3 (obese individuals), 4 (pregnant women), 5 (people with dark skin tone), 6 (athletes), RR=relative risk, RaR=rate ratio, OR=odds ratio, HR=hazard ratio, CI=confidence interval, BMD=bone mineral density, SMD=standardized mean difference, BMI=body mass index  
\*Direction of the effect size reported is always vitamin D supplementation versus comparator. \*\*A Measurement Tool to Assess systematic Reviews 1 (AMSTAR 1) is a quality assessment tool ranging from 0 (lowest quality) to 11 (highest quality). \*\*\*Some studies appear more than once in table as they address multiple outcomes/vitamin D modalities for a particular risk group.

Appendix 9. List of excluded studies from full text screening for clinical effectiveness of vitamin D testing (CRQa)

Author	Date	Title
<b>INCORRECT FCN AT RISK GROUP</b>		
Balfour, L., et al.	2014	Micronutrient deficiency and treatment adherence in a randomized controlled trial of micronutrient supplementation in ART-naive persons with HIV
Barr, R. J., et al.	2005	Screening elderly women for risk of future fractures--participation rates and impact on incidence of falls and fractures
Daniel, D., et al.	2011	Fibromyalgia--should we be testing and treating for vitamin D deficiency?
de Oliveira, J. F., et al.	2015	[Vitamin D in children and adolescents with sickle cell disease: an integrative review]
Derakhshanian, H., et al.	2015	Vitamin D and diabetic nephropathy: A systematic review and meta-analysis
Lee, M. T., et al.	2018	Randomized phase 2 trial of monthly vitamin D to prevent respiratory complications in children with sickle cell disease
Orgel, E., et al.	2017	A randomized controlled trial testing an adherence-optimized Vitamin D regimen to mitigate bone change in adolescents being treated for acute lymphoblastic leukemia
Verheyden, G. S., et al.	2013	Interventions for preventing falls in people after stroke
<b>INCORRECT SETTING - SOCIO-ECONOMIC DISSIMILAR TO CH</b>		
Chandrashekhara, S., et al.	2017	Role of vitamin D supplementation in improving disease activity in rheumatoid arthritis: An exploratory study
Nandal, R., et al.	2016	Comparison of cord blood vitamin D levels in newborns of vitamin D supplemented and unsupplemented pregnant women: a prospective, comparative study
Rostami, M., et al.	2018	Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial
Wallis, R. S., et al.	2016	Vitamin D as Adjunctive Host-Directed Therapy in Tuberculosis: A Systematic Review
<b>INCORRECT INTERVENTION – NOT VITAMIN D TESTING (I.E. OTHER SCREENING TEST, VITAMIN D SUPPLEMENTATION, ETC.)</b>		
Arnedo-Pena, A., et al.	2014	Vitamin D status and incidence of tuberculosis infection conversion in contacts of pulmonary tuberculosis patients: A prospective cohort study
Bjelakovic, G., et al.	2014	Vitamin D supplementation for prevention of mortality in adults
Brown, T. T., et al.	2015	Vitamin D supplementation does not affect metabolic changes seen with art initiation
Cameron, I. D., et al.	2018	Interventions for preventing falls in older people in care facilities and hospitals
Chakhtoura, M. T., et al.	2016	Hypovitaminosis D in bariatric surgery: a systematic review of observational studies
Chakhtoura, M., et al.	2017	Vitamin D Metabolism in Bariatric Surgery
Diao, N., et al.	2017	Effect of vitamin D supplementation on knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials
Ennis, J., et al.	2015	Clinical decision support improves physician guideline adherence for laboratory monitoring of chronic kidney disease: A matched cohort study
Farrokhyar, F., et al.	2017	Effects of Vitamin D Supplementation on Serum 25-Hydroxyvitamin D Concentrations and Physical Performance in Athletes: A Systematic Review and Meta-analysis of Randomized Controlled Trials
Fox, J., et al.	2011	Improvement in vitamin D deficiency following antiretroviral regime change: Results from the MONET trial
Geddes, J., et al.	2013	Evidence for the treatment of osteoporosis with vitamin d in residential care and in the community dwelling elderly
Goulao, B., et al.	2018	Cancer and vitamin D supplementation: a systematic review and meta-analysis
Hahn, D., et al.	2015	Interventions for metabolic bone disease in children with chronic kidney disease
Helland, I. B., et al.	2003	Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age
Huang, H. Y., et al.	2006	Multivitamin/mineral supplements and prevention of chronic disease
Izadpanah, M., et al.	2013	Potential benefits of vitamin D supplementation in critically ill patients
Jamka, M., et al.	2015	The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis
Jolliffe, D. A., et al.	2017	Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data
Jolliffe, D. A., et al.	2019	Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials
Martineau, A. R., et al.	2017	Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data
Murad, M. H., et al.	2011	Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis



Patel, R.;Rizvi, A. A.	2011	Vitamin D deficiency in patients with congestive heart failure: mechanisms, manifestations, and management
Rejnmark, L., et al.	2011	Effects of vitamin d on muscle function and performance: a review of evidence from randomized controlled trials
Rejnmark, L., et al.	2017	Non-skeletal health effects of vitamin D supplementation: A systematic review on findings from meta-analyses summarizing trial data
Swart, K. M., et al.	2018	Effects of vitamin D supplementation on markers for cardiovascular disease and type 2 diabetes: an individual participant data meta-analysis of randomized controlled trials
Tang, O., et al.	2018	Design Features of Randomized Clinical Trials of Vitamin D and Falls: A Systematic Review
Thorne-Lyman, A., et al.	2012	Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis
Yang, N., et al.	2015	Effects of vitamin D supplementation during pregnancy on neonatal vitamin D and calcium concentrations: a systematic review and meta-analysis
Zhao, J. G., et al.	2017	Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis
Zheng, Y., et al.	2013	Meta-analysis of long-term vitamin D supplementation on overall mortality
<b>INCORRECT COMPARATOR – NOT PLACEBO OR STANDARD CARE</b>		
Arvold, D. S., et al.	2009	Corelation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: A randomized controlled trial
Braddy, K. K., et al.	2009	Vitamin D Deficiency/Insufficiency Practice Patterns in a Veterans Health Administration Long-Term Care Population: A Retrospective Analysis
Datta, S., et al.	2002	Vitamin D deficiency in pregnant women from a non-European ethnic minority population - An interventional study
Hewitt, N. A., et al.	2013	Effects of cholecalciferol on functional, biochemical, vascular, and quality of life outcomes in hemodialysis patients
Hoeck, H. C., et al.	2009	Changes in 25-Hydroxyvitamin D3 to oral treatment with vitamin D3 in postmenopausal females with osteoporosis
Lake, J. E., et al.	2015	Success of Standard Dose Vitamin D Supplementation in Treated Human Immunodeficiency Virus Infection
Marckmann, P., et al.	2012	Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D
<b>INCORRECT OUTCOMES</b>		
Cadth., et al.	2014	Vitamin D toxicity associated with different vitamin D dosing regimens: safety
<b>INCORRECT STUDY TYPE – CONFERENCE ABSTRACT, REVIEW PAPER, LETTER, EDITORIAL</b>		
Abou-Raya, S., et al.	2013	A randomized controlled trial of early initiation of osteoporosis assessment and management in the acute setting of the fracture clinic
Bolland, M. J., et al.	2012	Should measurement of vitamin D and treatment of vitamin D insufficiency be routine in New Zealand?
Bolland, M. J., et al.	2015	Screening for Vitamin D deficiency
Carsley, S., et al.	2015	Cohort Profile: The Applied Research Group for Kids (TARGet Kids!)
Holick, M. F., et al.	2011	Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline
	2011	Committee Opinion No. 495: Vitamin D: Screening and Supplementation During Pregnancy
Hudson, J. Q.	2006	Secondary hyperparathyroidism in chronic kidney disease: focus on clinical consequences and vitamin D therapies
Kulie, T., et al.	2009	Vitamin D: an evidence-based review
Libman, H., et al.	2016	Should We Screen for Vitamin D Deficiency?: Grand Rounds Discussion From Beth Israel Deaconess Medical Center
Noe, K., et al.	2008	Bone health and antiseizure drugs: diagnosis and management
O'Connor, T., et al.	2014	Pelvic Insufficiency Fractures
Petering, R. ., et al.	2009	Exercise, fluid, and nutrition recommendations for the postgastric bypass exerciser
Shub, A., et al.	2019	Letter to the Editor: "Effectiveness of Prenatal Vitamin D Deficiency Screening and Treatment Program: A Stratified Randomized Field Trial"
Souberbielle, J. C., et al.	2012	When should we measure vitamin D concentration in clinical practice?
Yin, M., et al.	2012	Vitamin D, bone, and HIV infection
<b>INCORRECT STUDY TYPE – ECONOMICS</b>		
Pacis, M. M., et al.	2015	Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review
<b>INCORRECT STUDY DESIGN- NONRANDOMIZED RCTS, DIDN'T INCLUDE INTERVENTION OF SUPPLEMENTATION OR PLACEBO ARM TO UNDERSTAND THE IMPACT OF SCREENING VERSUS NO SCREENING</b>		
Aucoin, M., et al.	2013	Vitamin D status of refugees arriving in Canada: Findings from the calgary refugee health program
Bailey, B. A., et al.	2012	Vitamin D testing patterns among six Veterans Medical Centers in the southeastern United States: links with medical costs

Barton, D. W., et al.	2018	Rates of osteoporosis screening and treatment following vertebral fracture
Benitez-Aguirre, P. Z., et al.	2009	The natural history of vitamin D deficiency in African refugees living in Sydney
Kerezoudis, P., et al.	2016	Association Between Vitamin D Deficiency and Outcomes Following Spinal Fusion Surgery: A Systematic Review
<b>INCORRECT STUDY TYPE – SCREENING FOR VITAMIN D ONLY TO: REPORT PREVALENCE, VALIDATE SCREENING TOOL, ETC.</b>		
Davis, L. M., et al.	2010	Vitamin D Insufficiency Is Prevalent among Pregnant African American Adolescents
De Laine, K. M., et al.	2013	Prospective audit of vitamin D levels of women presenting for their first antenatal visit at a tertiary centre
Johri, N., et al.	2017	Vitamin D deficiency is prevalent among idiopathic stone formers, but does correction pose any risk
<b>LANGUAGE (NON-ENGLISH)</b>		
Feranchak, A. P., et al.	1999	Prospective, long-term study of fat-soluble vitamin status in children with cystic fibrosis identified by newborn screen
Gonzalez Jimenez, D., et al.	2015	[Vitamin D and Chronic Lung Colonization in Pediatric and Young Adults Cystic Fibrosis Patients]
Mengarelli, C., et al.	2015	Vitamin D screening in adults (Structured abstract)
<b>EPUB AHEAD OF PRINT (PHYSICAL AND ONLINE PUBLICATION NOT AVAILABLE)</b>		
Inkrott, BP. et al	2016	Hypovitaminosis D in Patients Undergoing Shoulder Arthroplasty: A Single-Center Analysis
Loh, HH. et al	2017	Effect of Vitamin D replacement in Primary Hyperparathyroidism with concurrent Vitamin D deficiency: a systematic review and meta-analysis
Eslami, O. et al	2018	Vitamin D and Cardiorespiratory Fitness in the General Population: A Systematic Review

#### Appendix 10. List of excluded economic studies of vitamin D testing from full text screening (CRQb)

Author	Year	Title	Reason for exclusion
Bailey et al.	2012	Vitamin D testing patterns among six Veterans Medical Centers in the southeastern United States: links with medical costs	incorrect comparator – different number of tests
Basatemeur et al.	2017	Costs of vitamin D testing and prescribing among children in primary care	incorrect population – over 75% of children not of dark skin tone
Bejjanki et al.	2018	The role of a best practice alert in the electronic medical record in reducing repetitive lab tests	incorrect PICOS - intervention electronic, not screening
Bilinski et al.	2013	Evidence of overtesting for vitamin D in Australia: an analysis of 4.5 years of Medicare Benefits Schedule (MBS) data	Non-economic study
Bilinski et al.	2012	The Vitamin D paradox: bone density testing in females aged 45 to 74 did not increase over a ten-year period despite a marked increase in testing for vitamin D	Although they do a subgroup analysis for 65-74, the subgroup analysis is more related to the clinical rather than the economics part of the report.
CADTH	2014	Vitamin D testing in the general population: clinical and cost-effectiveness and guidelines	This is a relevant HTA, but the only relevant economic evaluation the HTA reported was identified separately in our search (i.e. Lee et al). We Included this HTA in the clinical review of vitamin D testing.
Health Quality, Ontario	2010	Clinical utility of vitamin d testing: an evidence-based analysis	Non-economic study
Johnson et al.	2015	Yield and cost-effectiveness of laboratory testing to identify metabolic contributors to falls and fractures in older persons	incorrect intervention
Morgen et al.	2015	Inappropriate repeats of six common tests in a Canadian city: A population cohort study within a Laboratory Informatics framework	Incorrect population.
Naugler et al.	2017	Implementation of an intervention to reduce population-based screening for vitamin D deficiency: a cross-sectional study	Non-economic study
Pacis et al.	2015	Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review	incorrect population – women undergoing IVF, therefore not yet pregnant
Wei et al.	2014	Insignificant medium-term vitamin D status change after 25-hydroxyvitamin D testing in a large managed care population	Non-economic study

Appendix 11. List of excluded studies with reasons for exclusion, from full text screening for clinical effectiveness of vitamin D supplementation (URQ)

Author	Year	Title
<b>INCORRECT POPULATION (E.G. CARDIOVASCULAR, DIABETES, CANCER).</b>		
Alvarez, J. A., et al.	2012	Vitamin D supplementation in pre-dialysis chronic kidney disease: A systematic review
Annweiler, C., et al.	2013	Meta-analysis of memory and executive dysfunctions in relation to vitamin D
Antakia, R., et al.	2015	Effectiveness of Preventative and Other Surgical Measures on Hypocalcemia Following Bilateral Thyroid Surgery: A Systematic Review and Meta-Analysis
Ash, S., et al.	2014	Nutrition prescription to achieve positive outcomes in Chronic Kidney Disease: A systematic review
Bagur, M. J., et al.	2017	Influence of Diet in Multiple Sclerosis: A Systematic Review
Barber, G. A., et al.	2018	Effects and associations of nutrition in patients with venous leg ulcers: A systematic review
Batchelor, F., et al.	2010	What works in falls prevention after stroke?: A systematic review and meta-analysis
Bath-Hextall, F. J., et al.	2012	Dietary supplements for established atopic eczema
Beaudart, C., et al.	2017	Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review
Bergman, P., et al.	2013	Vitamin D and Respiratory Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Bjelakovic, G., et al.	2017	Vitamin D supplementation for chronic liver diseases in adults
Büttner, M., et al.	2017	Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review
Suetonia, C. P., et al.	2007	Interventions for preventing bone disease in kidney transplant recipients
Caini, S., et al.	2014	Vitamin D and melanoma and non-melanoma skin cancer risk and prognosis: a comprehensive review and meta-analysis
Carroll, C., et al.	2010	Supplemental calcium in the chemoprevention of colorectal cancer: A systematic review and meta-analysis
Charan, J., et al.	2012	Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis
Cheng, J., et al.	2012	Efficacy and safety of paricalcitol therapy for chronic kidney disease: A meta-analysis
Cicero, A. F. G., et al.	2017	Nutraceuticals and dietary supplements to improve quality of life and outcomes in heart failure patients
Daniel, D., et al.	2011	Fibromyalgia - should we be testing and treating for vitamin D deficiency?
De Borst, M. H., et al.	2013	Active vitamin D treatment for reduction of residual proteinuria: A systematic review
De Medeiros, M. C. S., et al.	2018	Dietary Intervention And Health In Patients With Systemic Lupus Erythematosus: A Systematic Review Of The Evidence
Edafe, O., et al.	2014	Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia
Fares, M. M., et al.	2015	Vitamin D supplementation in children with asthma: a systematic review and meta-analysis
Farinotti M., et al.	2012	Dietary interventions for multiple sclerosis
Feneis, J. F, et al.	2010	Role of vitamin D in blood pressure homeostasis
Fortmann, S. P., et al.	2013	Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. preventive services task force
Franco, A. S., et al.	2017	Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases
Franco, A. S., et al.	2017	Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases: A systematic review and meta-analysis
Gaikwad, M., et al.	2017	Does vitamin D supplementation alleviate chronic nonspecific musculoskeletal pain? A systematic review and meta-analysis
Gorham, E. D., et al.	2005	Vitamin D and prevention of colorectal cancer
Goulao, B., et al.	2018	Cancer and Vitamin D supplementation: A systematic review and meta-analysis
Gowda, U., et al.	2015	Vitamin D supplementation to reduce depression in adults: Meta-analysis of randomized controlled trials
Grace-Farfaglia, P, et al.	2015	Bones of contention: Bone mineral density recovery in celiac disease-A systematic review
Gysin, D. V., et al.	2016	Effect of Vitamin D3 supplementation on respiratory tract infections in healthy individuals: A systematic review and meta-Analysis of randomized controlled trials
H. Y. Huang, H. Y., et al.	2006	Multivitamin/mineral supplements and prevention of chronic disease

Hassan, A. B., et al.	2018	Therapeutic and maintenance regimens of vitamin D3 supplementation in healthy adults: A systematic review
Heine-Broring, R. C., et al.	2015	Dietary supplement use and colorectal cancer risk: A systematic review and meta-analyses of prospective cohort studies
Hempel, S., et al.	2017	A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis
Hossain, S., et al.	2019	Vitamin D and breast cancer: A systematic review and meta-analysis of observational studies
Hough, J. P., et al.	2010	Systematic review of interventions for low bone mineral density in children with cerebral palsy
Huang, C. M., et al.	2018	Effects of Vitamin D levels and supplementation on atopic dermatitis: A systematic review
Hujoel, P. P., et al.	2013	Vitamin D and dental caries in controlled clinical trials: Systematic review and meta-analysis
Ibanez-Vera, A. J., et al.	2018	Therapeutic physical exercise and supplements to treat fibromyalgia
Irlam, J. H., et al.	2010	Micronutrient supplementation in children and adults with HIV infection
Irlam, J. H., et al.	2013	Micronutrient supplementation for children with HIV infection
Izadpanah, M, et al.	2013	Potential benefits of vitamin D supplementation in critically ill patients
Izaks, G. J, et al.	2007	Fracture prevention with vitamin D supplementation: Considering the inconsistent results
J. Wang, J., et al.	2018	Efficacy and Safety of Vitamin D Supplementation for Pulmonary Tuberculosis: A Systematic Review and Meta-analysis
Jagannath V. A., et al.	2010	Vitamin D for the management of multiple sclerosis
Jagannath, V. A., et al.	2010	Vitamin D for the management of multiple sclerosis
Jagannath, V. A., et al.	2018	Vitamin D for the management of multiple sclerosis
James, E., et al.	2013	The effect of vitamin D-related interventions on multiple sclerosis relapses: A meta-analysis
James, H. I., et al.	2010	Micronutrient supplementation in children and adults with HIV infection
James, H. I., et al.	2013	Micronutrient supplementation for children with HIV infection
Janet, H. F., et al.	2014	Vitamin D supplementation for cystic fibrosis
Jat,K.R., et al.	2016	Vitamin D and lower respiratory tract infection in children: A systematic review and meta-analysis of randomized controlled trials
Jenkins, D. J. A., et al.	2018	Supplemental Vitamins and Minerals for CVD Prevention and Treatment
Joanne, H., et al.	1998	Calcium and vitamin D for corticosteroid-induced osteoporosis
Jolliffe,D. A., et al.	2017	Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data
Kim, G, et al.	2016	Vitamin D and atopic dermatitis: A systematic review and meta-analysis
Kim, Y, et al.	2014	Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: A meta-analysis
Lakshmi N. R., et al.	2005	Vitamins for epilepsy
Langlois, P. L., et al.	2018	Vitamin D supplementation in the critically ill: A systematic review and meta-analysis
Latham, N. K., et al.	2003	Effects of vitamin D supplementation on strength, physical performance, and falls in older persons: A systematic review
Lerch, C, et al.	2007	Interventions for the prevention of nutritional rickets in term born children
Li, L., et al.	2018	Efficacy of vitamin D in treatment of inflammatory bowel disease: A meta-analysis
Li, W., et al.	2018	Vitamin D supplementation during pregnancy and the risk of wheezing in offspring: a systematic review and dose-response meta-analysis
Li, Y. J., et al.	2018	Supplement intervention associated with nutritional deficiencies in autism spectrum disorders: a systematic review
Li, Y. J., et al.	2017	Dietary supplement for core symptoms of autism spectrum disorder: Where are we now and where should we go?
Lin, D, et al.	2007	Interventions for the treatment of decreased bone mineral density associated with HIV infection
Liu, Y., et al.	2018	Vitamin intake and pancreatic cancer risk reduction
Liu, Y., et al.	2015	Vitamin and multiple-vitamin supplement intake and incidence of colorectal cancer: a meta-analysis of cohort studies
Lourencetti, M, et al.	2018	Use of active metabolites of Vitamin D orally for the treatment of psoriasis
Lu, R. J.,et al.	2017	Effects of Vitamin D or its analogues on the mortality of patients with chronic kidney disease: An updated systematic review and meta-analysis
Luberto, C. M., et al.	2013	Integrative medicine for treating depression: An update on the latest evidence

Malihi, Z., et al.	2017	Noncalcemic adverse effects and withdrawals in randomized controlled trials of long-term vitamin D<sup>2</sup> or D<sup>3</sup> supplementation: A systematic review and meta-analysis
Malihi, Z., et al.	2018	Adverse events from large dose vitamin D supplementation taken for one year or longer
Malihi, Z., et al.	2016	Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of Vitamin D supplementation: A systematic review and meta-analysis
Mann, M. C., et al.	2015	Effect of oral vitamin D analogs on mortality and cardiovascular outcomes among adults with chronic kidney disease: A meta-analysis
Mao, S, et al.	2013	Vitamin D supplementation and risk of respiratory tract infections: A meta-analysis of randomized controlled trials
Marsden, J., et al.	2008	Can early onset bone loss be effectively managed in post-stroke patients? An integrative review of the evidence
Martineau, A. R., et al.	2016	Vitamin D for the management of asthma
McLaughlin, L., et al.	2018	Vitamin D for the treatment of multiple sclerosis: a meta-analysis
Meems, L. M. G., et al.	2011	Vitamin D Biology in Heart Failure: Molecular Mechanisms and Systematic Review
Minshull, C., et al.	2016	A Systematic Review of the Role of Vitamin D on Neuromuscular Remodelling Following Exercise and Injury
Misotti, A. M, et al.	2013	Vitamin supplement consumption and breast cancer risk: A review
Mitri, J., et al.	2011	Vitamin D and type 2 diabetes: A systematic review
Mocellin, S., et al.	2016	Breast Cancer Chemoprevention: A Network Meta-Analysis of Randomized Controlled Trials
Mohammad, Y.Y., et al.	2010	Vitamin D supplementation for preventing infections in children less than five years of age
Moroti, R., et al.	2012	Vitamin D an antimicrobial weapon against acute respiratory tract infections. A systematic review (2006- March 2011)
Moslehi, N., et al.	2017	Current Evidence on Associations of Nutritional Factors with Ovarian Reserve and Timing of Menopause: A Systematic Review
Murad, M. H., et al.	2012	Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis
Myung, S. K., et al.	2013	Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: Systematic review and meta-analysis of randomised controlled trials
Novak, I., et al.	2013	A systematic review of interventions for children with cerebral palsy: State of the evidence
Oliveira, J. F., et al.	2015	Vitamin D in children and adolescents with sickle cell disease: an integrative review
Palmer, S. C., et al.	2009	Vitamin D compounds for people with chronic kidney disease not requiring dialysis
Palmer, S. C., et al.	2009	Vitamin D compounds for people with chronic kidney disease requiring dialysis
Palmer, S. C., et al.	2007	Interventions for preventing bone disease in kidney transplant recipients
Palmer, S. C., et al.	2007	Meta-analysis: vitamin D compounds in chronic kidney disease
Palmer, S. C., et al.	2005	Interventions for preventing bone disease in kidney transplant recipients
Palmer, S.C., et al.	2009	Interventions for preventing bone disease in kidney transplant recipients
Papadimitropoulos, E., et al.	2002	VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women
Pittas, A. G., et al.	2010	Systematic review: Vitamin D and cardiometabolic outcomes
Pongcharoen, P, et al.	2016	An evidence-based review of systemic treatments for itch
Pozuelo-Moyano, B., et al.	2013	A systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in multiple sclerosis
Psaltopoulou, T., et al.	2018	Micronutrient Intake and Risk of Hematological Malignancies in Adults: A Systematic Review and Meta-analysis of Cohort Studies
Putzu, A., et al.	2017	Vitamin D and outcomes in adult critically ill patients. A systematic review and meta-analysis of randomized trials
Quinlivan, R., et al.	2014	Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V)
Ramdas, W. D., et al.	2018	The effect of vitamins on glaucoma: A systematic review and meta-analysis
Ranganathan, L. N., et al.	2009	Vitamins for epilepsy
Räßler, F., et al.	2017	Acrokeratosis paraneoplastica (Bazex syndrome) - a systematic review on risk factors, diagnosis, prognosis and management
Richman, E., et al.	2013	Review article: Evidence-based dietary advice for patients with inflammatory bowel disease
Richy, F., et al.	2005	Vitamin D analogs versus native vitamin D in preventing bone loss and osteoporosis-related fractures: A comparative meta-analysis
Rimmelzwaan, L. M., et al.	2016	Systematic Review of the Relationship between Vitamin D and Parkinson's Disease

Riverin, B. D., et al.	2015	Vitamin D supplementation for childhood asthma: A systematic review and meta-analysis
Rojas-Fernandez, C. H., et al.	2012	Assessing the potential adverse consequences of supplemental calcium on cardiovascular outcomes: Should we change our approach to bone health?
Rondanelli, M., et al.	2014	Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena
Rossi, R. E., et al.	2014	The role of dietary factors in prevention and progression of breast cancer
Rossi, R. E., et al.	2016	The role of dietary supplements in inflammatory bowel disease: A systematic review
Rueda, A. M. B., et al.	2015	Effects of vitamin D in the prevention of acute viral bronchiolitis: Systematic review
S. C. Palmer, S. C., et al.	2009	Vitamin D compounds for people with chronic kidney disease requiring dialysis
S. C. Palmer, S. C., et al.	2009	Vitamin D compounds for people with chronic kidney disease not requiring dialysis
Sawka, A. M., et al.	2010	A scoping review of strategies for the prevention of hip fracture in elderly nursing home residents
Schefft, C., et al.	2017	Efficacy of adding nutritional supplements in unipolar depression: A systematic review and meta-analysis
Schwingshackl, L., et al.	2017	Dietary Supplements and Risk of Cause-Specific Death, Cardiovascular Disease, and Cancer: A Systematic Review and Meta-Analysis of Primary Prevention Trials
Seida, J. C., et al.	2014	Effect of vitamin D<sup>3</sup> supplementation on improving glucose homeostasis and preventing diabetes: A systematic review and meta-analysis
Shaffer, J. A., et al.	2014	Vitamin d supplementation for depressive symptoms: A systematic review and meta-analysis of randomized controlled trials
Shang, X. H., et al.	2018	Effects of paricalcitol on cardiovascular outcomes and renal function in patients with chronic kidney disease: A meta-analysis
Showell, M. G., et al.	2017	Antioxidants for female subfertility
Silverberg, J. I., et al.	2014	Atopic dermatitis: An evidence-based treatment update
Soe Htoo Htoo, K., et al.	2013	Vitamin D supplementation for sickle cell disease
Soe, H. H. K., et al.	2017	Vitamin D supplementation for sickle cell disease
Song, G. G., et al.	2012	Association between vitamin D intake and the risk of rheumatoid arthritis: A meta-analysis
Sousa, J. R., et al.	2017	Effect of vitamin D supplementation on patients with systemic lupus erythematosus: a systematic review
Stewart, S., et al.	2012	Building osteoporosis prevention into dental practice
Straube, S., et al.	2015	Vitamin D for the treatment of chronic painful conditions in adults
Straube, S., et al.	2010	Vitamin D and chronic pain in immigrant and ethnic minority patients: investigation of the relationship and comparison with native western populations
Swart, K. M. A., et al.	2018	Effects of Vitamin D supplementation on markers for cardiovascular disease and type 2 diabetes: An individual participant data meta-analysis of randomized controlled trials
Thornton, J., et al.	2008	A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management
Tomlinson, P. B., et al.	2015	Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis
Touvier, M., et al.	2011	Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk
Tripkovic, L., et al.	2012	Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis
Tuchinda, P., et al.	2018	Relationship between vitamin D and chronic spontaneous urticaria: A systematic review 11 Medical and Health Sciences 1103 Clinical Sciences 11 Medical and Health Sciences 1117 Public Health and Health Services
Varela-Lopez, A., et al.	2018	Nutraceuticals in Periodontal Health: A Systematic Review on the Role of Vitamins in Periodontal Health Maintenance
Veettil, S. K., et al.	2018	Efficacy and safety of chemopreventive agents on colorectal cancer incidence and mortality: Systematic review and network meta-analysis
Veronese, N., et al.	2015	Vitamin D status in anorexia nervosa: A meta-analysis
Vieira, B. L., et al.	2016	Complementary and Alternative Medicine for Atopic Dermatitis: An Evidence-Based Review
Whitton, M. E., et al.	2015	Interventions for vitiligo
Winzenberg, T., et al.	2011	Effects of vitamin D supplementation on bone density in healthy children: Systematic review and meta-analysis
Wu, Y., et al.	2009	Efficacy and safety of tacalcitol and calcitriol on vitiligo: a systematic review
Wu, Z., et al.	2016	Effect of vitamin D supplementation on pain: A systematic review and meta-analysis

Wu, Z., et al.	2016	Effect of vitamin D supplementation on pain: A systematic review and meta-analysis
X. H. Li, X.H., et al.	2015	Effect of active Vitamin D on cardiovascular outcomes in predialysis chronic kidney diseases: A systematic review and meta-analysis
Xu, L., et al.	2013	Impact of Vitamin D on Chronic Kidney Diseases in Non-Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials
Yakoob, M. Y., et al.	2016	Vitamin D supplementation for preventing infections in children under five years of age
Yong, W. C., et al.	2017	Effect of vitamin D supplementation in chronic widespread pain: a systematic review and meta-analysis
Yuen, H. K., et al.	2014	Optimal management of fatigue in patients with systemic lupus erythematosus: A systematic review
Zadro, J. R., et al.	2018	Is vitamin d supplementation effective for low back pain? A systematic review and meta-analysis
Zhang, H., et al.	2015	Vitamin D Deficiency and Increased Risk of Bladder Carcinoma: A Meta-Analysis
Zhang, L. R., et al.	2013	Vitamin and mineral supplements and thyroid cancer: A systematic review
Zhang, X., et al.	2017	Plasma 25-hydroxyvitamin D levels, vitamin D intake, and pancreatic cancer risk or mortality: A meta-analysis
Zheng, C., et al.	2018	The efficacy of vitamin D in multiple sclerosis: A meta-analysis
Zheng, S.H., et al.	2013	Vitamin D supplementation and mortality risk in chronic kidney disease: A meta-analysis of 20 observational studies
Zheng, Y., et al.	2013	Meta-analysis of long-term vitamin D supplementation on overall mortality
Zhu, B., et al.	2015	Vitamin D deficiency is associated with the severity of COPD: A systematic review and meta-analysis
Zittermann, A, et al.	2018	Vitamin D status, supplementation and cardiovascular disease
<b>INCORRECT SETTING (E.G. LOW OR MIDDLE INCOME COUNTRY)</b>		
Abba, K., et al.	2008	Nutritional supplements for people being treated for active tuberculosis
Akbari, M., et al.	2017	The Effects of Vitamin D Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Arain, N., et al.	2015	Vitamin D and the prevention of preeclampsia: A systematic review
Das, R. R., et al.	2013	Vitamin D supplementation for the treatment of acute childhood pneumonia: A systematic review
Fu, Z. M., et al.	2018	Vitamins supplementation affects the onset of preeclampsia
Grobler, L., et al.	2016	Nutritional supplements for people being treated for active tuberculosis
Hofmeyr, G. J., et al.	2014	Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems
Hofmeyr, G. J., et al.	2018	Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems
Jahanjoo, F., et al.	2018	Maternal and neonatal metabolic outcomes of Vitamin D supplementation in gestational diabetes mellitus: A systematic review and meta-analysis
Khaing, W., et al.	2017	Calcium and vitamin D supplementation for prevention of preeclampsia: A systematic review and network meta-analysis
Kim, M. J., et al.	2016	Vitamin D status and efficacy of vitamin D supplementation in atopic dermatitis: A systematic review and meta-analysis
Kua, K. P., et al.	2017	Complementary and alternative medicine for the treatment of bronchiolitis in infants: A systematic review
L. Christian, L., et al.	2007	Interventions for the prevention of nutritional rickets in term born children
Palacios, C., et al.	2016	Vitamin D supplementation during pregnancy: Updated meta-analysis on maternal outcomes
Pojsupap, S., et al.	2015	Efficacy of high-dose vitamin D in pediatric asthma: A systematic review and meta-analysis
Roth, D. E., et al.	2017	Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials
Shen, L., et al.	2015	Associations between vitamin D status, supplementation, outdoor work and risk of parkinson's disease: A meta-analysis assessment
Sinclair, D., et al.	2011	Nutritional supplements for people being treated for active tuberculosis
Sparling, T. M., et al.	2017	The role of diet and nutritional supplementation in perinatal depression: a systematic review
Sutaria, N., et al.	2014	Vitamin D status, receptor gene polymorphisms, and supplementation on tuberculosis: A systematic review of case-control studies and randomized controlled trials
Tabrizi, R., et al.	2017	The effects of vitamin D supplementation on metabolic profiles and liver function in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials
Villar, L. M., et al.	2013	Association between vitamin D and hepatitis C virus infection: A meta-analysis

Visser, M. E., et al.	2017	Micronutrient supplementation in adults with HIV infection
Wallis, R. S., et al.	2016	Vitamin D as adjunctive host-directed therapy in tuberculosis: A systematic review
Wu, H. X., et al.	2018	Effects of vitamin D supplementation on the outcomes of patients with pulmonary tuberculosis: A systematic review and meta-analysis
Xia, J. Y., et al.	2014	Impact of vitamin D supplementation on the outcome of tuberculosis treatment: A systematic review and meta-analysis of randomized controlled trials
Xiao, L., et al.	2015	Vitamin D supplementation for the prevention of childhood acute respiratory infections: A systematic review of randomised controlled trials
Zhang, Y., et al.	2018	Vitamin D and gestational diabetes mellitus: a systematic review based on data free of Hawthorne effect
Zhou, S. S., et al.	2017	Vitamin D and risk of preterm birth: Up-to-date meta-analysis of randomized controlled trials and observational studies
<b>INCORRECT INTERVENTION – NOT VITAMIN D SUPPLEMENTATION</b>		
Agbalalah, T., et al.	2017	Impact of vitamin D supplementation on endothelial and inflammatory markers in adults: A systematic review
Allen, C. S., et al.	2016	Bisphosphonates for steroid-induced osteoporosis
Artaza-Artabe, I., et al.	2016	The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review
Ashcroft, D. M., et al.	2000	Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis
Autier, P., et al.	2012	A systematic review: Influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration
Beckhaus, A. A., et al.	2015	Maternal nutrition during pregnancy and risk of asthma, wheeze, and atopic diseases during childhood: A systematic review and meta-analysis
Bell, K., et al.	2014	Effect of a dedicated osteoporosis health professional on screening and treatment in outpatients presenting with acute low trauma non-hip fracture: A systematic review
Bhandari, N., et al.	2001	Effect of micronutrient supplementation on linear growth of children
Bolland, M. J., et al.	2011	Calcium supplements with or without vitamin D and risk of cardiovascular events: Reanalysis of the Women's Health Initiative limited access dataset and meta-analysis
Brandao, C. M., et al.	2008	Treatment of postmenopausal osteoporosis in women: a systematic review
Cassim, R., et al.	2015	The role of circulating 25 hydroxyvitamin D in asthma: A systematic review
Chen, F., et al.	2015	Association of vitamin C, vitamin D, vitamin E and risk of bladder cancer: a dose-response meta-analysis
Chen, H., et al.	2018	25-Hydroxyvitamin D Levels and the Risk of Dementia and Alzheimer's Disease: A Dose-Response Meta-Analysis
Chen, P., et al.	2010	Meta-analysis of vitamin D, calcium and the prevention of breast cancer
Clay, P. G., et al.	2008	Valid treatment options for osteoporosis and osteopenia in HIV-infected persons
Cook, L. S., et al.	2010	A systematic literature review of vitamin D and ovarian cancer
Coussement, J., et al.	2008	Interventions for preventing falls in acute- and chronic-care hospitals: a systematic review and meta-analysis
Creo, A. L., et al.	2017	Nutritional rickets around the world: an update
Davidson, Z. E., et al.	2009	A review of nutrition in Duchenne muscular dystrophy
de Jager, M. E. A., et al.	2010	Efficacy and safety of treatments for childhood psoriasis: A systematic literature review
de Menezes, A. F., et al.	2017	Pharmacologic Treatment of Vitiligo in Children and Adolescents: A Systematic Review
de Menezes, A. F., et al.	2017	Pharmacologic Treatment of Vitiligo in Children and Adolescents: A Systematic Review
de Waure, C., et al.	2015	Systematic review of studies investigating the association between dietary habits and cutaneous malignant melanoma
Dong, J. Y., et al.	2013	Vitamin D intake and risk of type 1 diabetes: A meta-analysis of observational studies
Elliot-Gibson, V., et al.	2004	Practice patterns in the diagnosis and treatment of osteoporosis after a fragility fracture: A systematic review
Eui Geum, Oh, et al.	2012	A systematic review of the effectiveness of lifestyle interventions for improving bone health in women at high risk of osteoporosis
Farrington, E., et al.	2013	Relationship of Vitamin D3 Deficiency to Depression in Older Adults: A Systematic Review of the Literature From 2008-2013
Fazel, N., et al.	2015	Cutaneous lichen planus: A systematic review of treatments
Freedman, R., et al.	2018	Prenatal Primary Prevention of mental illness by micronutrient supplements in pregnancy
Galthen-Sørensen, M., et al.	2014	Maternal 25-hydroxyvitamin D level and fetal bone growth assessed by ultrasound: a systematic review



Ganesh, A., et al.	2013	The case for vitamin D supplementation in multiple sclerosis
Gaugris, S., et al.	2005	Vitamin D inadequacy among post-menopausal women: A systematic review
Gorter, E. A., et al.	2014	The role of vitamin D in human fracture healing: A systematic review of the literature
Griffiths, C. E., et al.	2000	A systematic review of treatments for severe psoriasis
Hendriks, A. G. M., et al.	2013	Efficacy and safety of combinations of first-line topical treatments in chronic plaque psoriasis: a systematic literature review
Khayatzadeh, S., et al.	2015	Vitamin D intake, serum Vitamin D levels, and risk of gastric cancer: A systematic review and meta-analysis
Kriegel, M. A., et al.	2011	Does Vitamin D Affect Risk of Developing Autoimmune Disease?: A Systematic Review
Lee, R. H., et al.	2010	A review of the effect of anticonvulsant medications on bone mineral density and fracture risk
Lee, Y. Q., et al.	2018	The relationship between maternal nutrition during pregnancy and offspring kidney structure and function in humans: A systematic review
Leung, B. M. Y., et al.	2011	Does prenatal micronutrient supplementation improve children's mental development? A systematic review
Lippuner, K., et al.	2003	Medical treatment of vertebral osteoporosis
Liu, J., et al.	2017	Meta-analysis of the correlation between vitamin D and lung cancer risk and outcomes
Liu, W., et al.	2015	Meta-analysis of osteoporosis: Fracture risks, medication and treatment
Liu, X., et al.	2018	Which supplements can I recommend to my osteoarthritis patients?
Lock, C. A., et al.	2006	Lifestyle interventions to prevent osteoporotic fractures: a systematic review
Malik, R., et al.	2007	Vitamin D and secondary hyperparathyroidism in the institutionalized elderly: a literature review
Martínez-Domínguez, S. J., et al.	2018	Systematic review and meta-analysis of Spanish studies regarding the association between maternal 25-hydroxyvitamin D levels and perinatal outcomes
Mason Anne, R., et al.	2013	Topical treatments for chronic plaque psoriasis
McKay, K. A., et al.	2017	Factors associated with onset, relapses or progression in multiple sclerosis: A systematic review
Miller Brendan, J., et al.	2013	Dietary supplements for preventing postnatal depression
Misra, M., et al.	2016	State of the art systematic review of bone disease in anorexia nervosa
Morfeld, J. C., et al.	2017	Patient education in osteoporosis prevention: a systematic review focusing on methodological quality of randomised controlled trials
Munoz Fernandez, S. S., et al.	2017	Nutritional Strategies in the Management of Alzheimer Disease: Systematic Review With Network Meta-Analysis
Nurmatov, U., et al.	2011	Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis
Omair, M. A., et al.	2013	Low bone density in systemic sclerosis. a systematic review
Pacheco-González, R. M., et al.	2018	Prenatal vitamin D status and respiratory and allergic outcomes in childhood: A meta-analysis of observational studies
Patel, N. U., et al.	2017	Calcipotriene/betamethasone dipropionate for the treatment of psoriasis vulgaris: an evidence-based review
Penner, J., et al.	2018	The impact of Vitamin D supplementation on musculoskeletal health outcomes in children, adolescents, and young adults living with HIV: A systematic review
Pfeifer, M., et al.	2010	Musculoskeletal rehabilitation after hip fracture: A review
Pourmasoumi, M., et al.	2018	Association of omega-3 fatty acid and epileptic seizure in epileptic patients: A systematic review
Rabenda, V., et al.	2011	Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression
Robien, K., et al.	2013	Drug-vitamin D interactions: A systematic review of the literature
Ruxton, C. H., et al.	2016	Role of fatty acids and micronutrients in healthy ageing: a systematic review of randomised controlled trials set in the context of European dietary surveys of older adults
Scragg, R., et al.	2011	Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood
Seamans, K. M., et al.	2009	Existing and potentially novel functional markers of vitamin D status: A systematic review
Senti, J., et al.	2012	Maternal Vitamin D Status as a Critical Determinant in Gestational Diabetes
Showell, M. G., et al.	2013	Antioxidants for female subfertility
Tang, O., et al.	2018	Design features of randomized clinical trials of vitamin D and falls: A systematic review
van der Schaft, J., et al.	2013	The association between vitamin D and cognition: A systematic review

Vecchio, M., et al.	2010	Interventions for treating sexual dysfunction in patients with chronic kidney disease
Wang, L., et al.	2012	Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies
Weidner, T., et al.	2017	Primary Localized Cutaneous Amyloidosis: A Systematic Treatment Review
Weidner, T., et al.	2017	Treatment of Porokeratosis: A Systematic Review
Wu, W., et al.	2016	The association between serum vitamin D levels and age-related macular degeneration: A systematic meta-analytic review
Yakoob, M. Y., et al.	2017	Nutrition (Micronutrients) in Child Growth and Development: A Systematic Review on Current Evidence, Recommendations and Opportunities for Further Research
Zgaga, L., et al.	2016	Markers of Vitamin D Exposure and Esophageal Cancer Risk: A Systematic Review and Meta-analysis
Zheng, Y. T., et al.	2015	A meta-analysis of high dose, intermittent vitamin D supplementation among older adults
<b>INCORRECT INTERVENTION – VITAMIN D WITH FORTIFICATION IN FOODS</b>		
Antico, A., et al.	2012	Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature
Aryan, Z., et al.	2017	Vitamin D status, aeroallergen sensitization, and allergic rhinitis: A systematic review and meta-analysis
Chowdhury, R., et al.	2014	Vitamin D and risk of cause specific death: Systematic review and meta-analysis of observational cohort and randomised intervention studies
Das, J. K., et al.	2013	Micronutrients food fortification and its impact on woman and child health: a systematic review
Duranton, F., et al.	2013	Vitamin D treatment and mortality in chronic kidney disease: A systematic review and meta-analysis
Garcia-Larsen, V., et al.	2018	Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis
Goodwill, A. M., et al.	2017	A Systematic Review and Meta-Analysis of The Effect of Low Vitamin D on Cognition
Roberts, J. L., et al.	2017	The Impact of Nutritional Interventions beyond the First 2 Years of Life on Linear Growth: A Systematic Review and Meta-Analysis
Su, G., et al.	2019	Vitamin D deficiency and treatment versus risk of infection in end-stage renal disease patients under dialysis: a systematic review and meta-analysis
<b>INCORRECT COMPARATOR – NOT PLACEBO OR STANDARD CARE</b>		
Avenell, A., et al.	2000	Nutritional supplementation for hip fracture aftercare in the elderly
Avenell, A., et al.	2004	Nutritional supplementation for hip fracture aftercare in the elderly
Avenell, A., et al.	2005	Nutritional supplementation for hip fracture aftercare in older people
Avenell, A., et al.	2006	Nutritional supplementation for hip fracture aftercare in older people
Avenell, A., et al.	2010	Nutritional supplementation for hip fracture aftercare in older people
Avenell, A., et al.	2016	Nutritional supplementation for hip fracture aftercare in older people
Bolignano, D., et al.	2015	Interventions for preventing the progression of autosomal dominant polycystic kidney disease
Chen, L. X., et al.	2015	Comparison of bone mineral density in lumbar spine and fracture rate among eight drugs in treatments of osteoporosis in men: A network meta-analysis
Christensen, N., et al.	2017	Infant Respiratory Tract Infections or Wheeze and Maternal Vitamin D in Pregnancy: A Systematic Review
de Waard, M., et al.	2017	Optimal nutrition in lactating women and its effect on later health of offspring: A systematic review of current evidence and recommendations (EarlyNutrition project)
Gandini, S., et al.	2009	Vitamin D and skin cancer: A meta-analysis
Guyatt, G., et al.	2002	Meta-analyses of therapies for postmenopausal osteoporosis
Hoffmann, M. R., et al.	2015	Vitamin D supplementation and health-related quality of life: a systematic review of the literature
Mazess, R. B., et al.	2003	A review of intravenous versus oral vitamin D hormone therapy in hemodialysis patients
Nicholson, I., et al.	2012	Vitamin D as a therapy for colitis: A systematic review
Ranganathan, L. N., et al.	2005	Vitamins for epilepsy
Richy, F., et al.	2004	Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: A meta-analysis of their effects on bone mineral density and fracture rate
Sridharan, K., et al.	2018	Interventions for Improving Bone Mineral Density and Reducing Fracture Risk in Osteogenesis Imperfecta: A Mixed Treatment Comparison Network Meta-analysis of Randomized Controlled Clinical Trials
Vidot, H., et al.	2014	Systematic review: The treatment of muscle cramps in patients with cirrhosis

Xie, Y., et al.	2017	Comparative efficacy and safety of paricalcitol versus Vitamin D receptor activators for dialysis patients with secondary hyperparathyroidism: A meta-analysis of randomized controlled trials
Xu, Z., et al.	2016	Treatment of osteoporosis with eldecalcitol, a new vitamin D analog: A comprehensive review and meta-analysis of randomized clinical trials
Yang, Y., et al.	2018	Effect of different dose of vitamin D supplementation on preterm infants- an updated meta-analysis
Yepes-Nunez, J. J., et al.	2018	Vitamin D supplementation in primary allergy prevention: Systematic review of randomized and non-randomized studies
<b>INCORRECT OUTCOMES (E.G. METABOLIC)</b>		
Aloia, J. F., et al.	2006	Optimal vitamin D status and serum parathyroid hormone concentrations in African American women
Altieri, B., et al.	2017	Does vitamin D play a role in autoimmune endocrine disorders? A proof of concept
Amin, S., et al.	2002	The comparative efficacy of drug therapies used for the management of corticosteroid-induced osteoporosis: A meta-regression
Bassatne, A., et al.	2019	Vitamin D supplementation in obesity and during weight loss: a review of randomized controlled trials
Basutkar, R. S., et al.	2019	Vitamin D supplementation in patients with iron deficiency anaemia: A systematic review and a meta-analysis
Bath-Hextall, J. F., et al.	2012	Dietary supplements for established atopic eczema
Beveridge, L. A., et al.	2018	Effect of vitamin D supplementation on markers of vascular function: A systematic review and individual participant meta-analysis
Beveridge, L. A., et al.	2015	Effect of vitamin D supplementation on blood pressure a systematic review and meta-analysis incorporating individual patient data
Bjorkman, M., et al.	2008	Vitamin D supplementation has minor effects on parathyroid hormone and bone turnover markers in vitamin D - Deficient bedridden older patients
Bjorkman, M., et al.	2009	Responses of parathyroid hormone to vitamin D supplementation: A systematic review of clinical trials
Brett, N. R., et al.	2018	Effect of Vitamin D Supplementation, Food Fortification, or Bolus Injection on Vitamin D Status in Children Aged 2-18 Years: A Meta-Analysis
Butler, M., et al.	2018	Over-the-counter supplement interventions to prevent cognitive decline, mild cognitive impairment, and clinical Alzheimer-type dementia
Calton, E. K., et al.	2017	The impact of cholecalciferol supplementation on the systemic inflammatory profile: A systematic review and meta-analysis of high-quality randomized controlled trials
Cernaro, V., et al.	2014	New therapeutic strategies under development to halt the progression of renal failure
Chakhtoura, M. T., et al.	2016	Hypovitaminosis D in bariatric surgery: A systematic review of observational studies
Challoumas, D., et al.	2014	Vitamin D supplementation and lipid profile: What does the best available evidence show?
Chanson, P., et al.	2014	[Vitamin D supplementation: for and against in the BMJ!]
Chen, C., et al.	2017	The Effects of Dietary Calcium Supplements Alone or With Vitamin D on Cholesterol Metabolism: A Meta-Analysis of Randomized Controlled Trials
Chen, N., et al.	2014	Effect of vitamin D supplementation on the level of circulating high-sensitivity C-reactive protein: A meta-analysis of randomized controlled trials
Childs, K., et al.	2011	Effects of vitamin D deficiency and combination antiretroviral therapy on bone in HIV-positive patients. []
Custodero, C., et al.	2018	Evidence-based nutritional and pharmacological interventions targeting chronic low-grade inflammation in middle-age and older adults: A systematic review and meta-analysis
Dennis, V. C., et al.	2006	Doxercalciferol treatment of secondary hyperparathyroidism
Dinca, M., et al.	2016	Does vitamin D supplementation alter plasma adipokines concentrations? A systematic review and meta-analysis of randomized controlled trials
Dix, C. F., et al.	2017	A Systematic Review: Vitamin D Status and Sleeve Gastrectomy
Estébanez, N., et al.	2018	Vitamin D exposure and Risk of Breast Cancer: a meta-analysis
Fehlings, D., et al.	2012	Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: A systematic review
Ferguson, J. H., et al.	2012	Vitamin D supplementation for cystic fibrosis
Ferguson, J. H., et al.	2014	Vitamin D supplementation for cystic fibrosis
Fernandez, H., et al.	2018	Vitamin D supplementation for bone health in adults with epilepsy: A systematic review
Filgueiras, M. S., et al.	2018	Vitamin D status, oxidative stress, and inflammation in children and adolescents: A systematic review
Ford, J. A., et al.	2014	Cardiovascular disease and vitamin D supplementation: Trial analysis, systematic review, and meta-analysis
Gallagher, B., et al.	2015	Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents

Geary, D. F., et al.	2010	Interventions for bone disease in children with chronic kidney disease
George, P. S., et al.	2012	Effect of vitamin D supplementation on glycaemic control and insulin resistance: A systematic review and meta-analysis
Golzarand, M., et al.	2018	Vitamin D supplementation and body fat mass: a systematic review and meta-analysis
Golzarand, M., et al.	2016	Effect of vitamin D3 supplementation on blood pressure in adults: An updated meta-analysis
Gruppen, M. P., et al.	2013	Prevention of steroid-induced low bone mineral density in children with renal diseases: A systematic review
Hahn, D., et al.	2015	Interventions for metabolic bone disease in children with chronic kidney disease
Han, T., et al.	2013	Meta-analysis: The efficacy and safety of paricalcitol for the treatment of secondary hyperparathyroidism and proteinuria in chronic kidney disease
Himbert, C., et al.	2017	A systematic review of the interrelation between diet- and surgery-induced weight loss and vitamin D status
Hosseini, B., et al.	2017	Association between Micronutrients Intake/Status and Carotid Intima Media Thickness: A Systematic Review
Huang, L., et al.	2016	Vitamin D and micro-inflammatory state in hemodialysis patients a mini review and meta-analysis
Hussin, A. M., et al.	2017	Effects of vitamin D supplementation on endothelial function: a systematic review and meta-analysis of randomised clinical trials
Jamka, M., et al.	2015	The effect of vitamin D supplementation on insulin and glucose metabolism in overweight and obese individuals: systematic review with meta-analysis
Jamka, M., et al.	2016	The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis
Jayasena, A., et al.	2015	Treatment of glucocorticoid-induced low bone mineral density in children: A systematic review
Jolfaie, N. R., et al.	2016	The association between vitamin D and health outcomes in women: A review on the related evidence
Jolliffe, D. A., et al.	2013	Vitamin D in the prevention of acute respiratory infection: Systematic review of clinical studies
Jorde, R., et al.	2010	No significant effect on bone mineral density by high doses of vitamin D <sub>3</sub> given to overweight subjects for one year
Joris, P. J., et al.	2015	Effects of supplementation with the fat-soluble Vitamins E and D on fasting flow-mediated vasodilation in adults: A meta-analysis of randomized controlled trials
Kandula, P., et al.	2011	Vitamin D supplementation in chronic kidney disease: A systematic review and meta-analysis of observational studies and randomized controlled trials
Karras, S., et al.	2016	Hypovitaminosis D in pregnancy in the Mediterranean region: A systematic review
Kearns, M. D., et al.	2014	Large, single-dose, oral vitamin D supplementation in adult populations: A systematic review
Kunutsor, S. K., et al.	2014	Vitamin D and high blood pressure: Causal association or epiphenomenon?
Lassi, Z. S., et al.	2017	Systematic review on evidence-based adolescent nutrition interventions
Li, Z., et al.	2018	Vitamin D supplementation for the prevention of vitamin D deficiency after bariatric surgery: a systematic review and meta-analysis
Lotito, A., et al.	2017	Serum parathyroid hormone responses to vitamin D supplementation in overweight/obese adults: A systematic review and meta-analysis of randomized clinical trials
Lundwall, K., et al.	2018	Treating endothelial dysfunction with vitamin D in chronic kidney disease: A meta-analysis
Manousopoulou, A., et al.	2015	Vitamin D and cardiovascular risk among adults with obesity: A systematic review and meta-analysis
Marik, P. E., et al.	2012	Do dietary supplements have beneficial health effects in industrialized nations: What is the evidence?
Mateussi, M., et al.	2017	What do Cochrane systematic reviews say about interventions for vitamin D supplementation?
Mazidi, M., et al.	2017	The impact of vitamin D supplement intake on vascular endothelial function; a systematic review and meta-analysis of randomized controlled trials
McCullough, P. A., et al.	2004	Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: A systematic review
McNally, J. D., et al.	2015	Rapid normalization of vitamin D levels: A meta-analysis
Melek, J., et al.	2014	Efficacy and safety of medical therapy for low bone mineral density in patients with inflammatory bowel disease: A meta-analysis and systematic review
Mirhosseini, N., et al.	2018	Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: A meta-analysis
Mora, N., et al.	2013	25-Hydroxyvitamin D Supplementation and BMI Change: A Meta-Analysis of Randomized Controlled Trials
Moslehi, N., et al.	2015	Determinants of parathyroid hormone response to Vitamin D supplementation: A systematic review and meta-analysis of randomised controlled trials
Nahas, R., et al.	2008	Complementary and alternative medicine approaches to blood pressure reduction: An evidence-based review

Nama, N., et al.	2016	A systematic review of pediatric clinical trials of high dose vitamin D
Nashat, S. M., et al.	2018	Effectiveness of vitamin D in monitoring of pediatric hypertension: Systematic review and meta-analysis
Neil Thomas, G., et al.	2012	Hyperglycaemia and vitamin D: A systematic overview
Nisar, M. K., et al.	2013	What do we know about juvenile idiopathic arthritis and vitamin D? A systematic literature review and meta-analysis of current evidence
Okereke, O.I., et al.	2016	The role of Vitamin D in the prevention of late-life depression
Pittas, A. G., et al.	2007	Review: The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis
Pojsupap, S., et al.	2015	Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis
Poolsup, N., et al.	2016	Effect of vitamin D supplementation on insulin resistance and glycaemic control in prediabetes: A systematic review and meta-analysis
Qi, D., et al.	2017	The effect of vitamin D supplementation on hypertension in non-CKD populations: A systemic review and meta-analysis
Reid, I. R., et al.	2014	Effects of vitamin D supplements on bone mineral density: A systematic review and meta-Analysis
Rejnmark, L., et al.	2017	Non-skeletal health effects of Vitamin D supplementation: A systematic review on findings from meta-Analyses summarizing trial data
Rodriguez, A. J., et al.	2016	Effect of Vitamin D supplementation on measures of arterial stiffness: A systematic review and meta-analysis of randomized controlled trials
Sanabria, A., et al.	2011	Routine postoperative administration of vitamin D and calcium after total thyroidectomy: A meta-analysis
Sanadgol, N., et al.	2017	Recent updates in imperative natural compounds for healthy brain and nerve function: A systematic review of implications for multiple sclerosis
Sarathy, H., et al.	2015	The effects of short-term vitamin D supplementation on glucose metabolism in dialysis patients: a systematic review and meta-analysis
Sepidarkish, M., et al.	2019	The effect of vitamin D supplementation on oxidative stress parameters: A systematic review and meta-analysis of clinical trials
Shab-Bidar, S., et al.	2014	Serum 25(OH)D response to vitamin D<sup>3</sup> supplementation: A meta-regression analysis
Shah, V. N., et al.	2014	Effect of 25 (OH) D replacements in patients with primary hyperparathyroidism (PHPT) and coexistent vitamin D deficiency on serum 25(OH) D, calcium and PTH levels: A meta-analysis and review of literature
Sharifi, N., et al.	2017	Vitamin D Supplementation and Non-alcoholic fatty liver disease: A Critical and Systematic Review of Clinical Trials
Shu, L., et al.	2018	Effect of vitamin D supplementation on blood pressure parameters in patients with vitamin D deficiency: a systematic review and meta-analysis
Silk, L. N., et al.	2015	The effect of calcium or calcium and Vitamin D supplementation on bone mineral density in healthy males: A systematic review and meta-analysis
Spedding, S., et al.	2014	Vitamin D and depression: A systematic review and meta-analysis comparing studies with and without biological flaws
Sprague, S., et al.	2016	What is the role of Vitamin D supplementation in acute fracture patients? A systematic review and meta-analysis of the prevalence of Hypovitaminosis D and supplementation efficacy
Stojanovic, M., et al.	2015	Vitamin D Versus Placebo in Improvement of Endothelial Dysfunction: A Meta-Analysis of Randomized Clinical Trials
Tai, V., et al.	2015	Calcium intake and bone mineral density: Systematic review and meta-analysis
Thiele, D. K., et al.	2013	Maternal vitamin D supplementation to meet the needs of the breastfed infant: a systematic review
Upala, S., et al.	2016	Effect of cholecalciferol supplementation on arterial stiffness: a systematic review and meta-analysis
Von Domarus, C., et al.	2011	How much vitamin D Do we need for skeletal health?
Vondracek, S. F., et al.	2011	Combination vitamin D therapy in stage 5 chronic kidney disease
Vuichard Gysin, D., et al.	2016	Effect of Vitamin D3 Supplementation on Respiratory Tract Infections in Healthy Individuals: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Wang, H., et al.	2012	Influence of vitamin D supplementation on plasma lipid profiles: A meta-analysis of randomized controlled trials
Whiting, S. J., et al.	2015	Moderate amounts of vitamin d3 in supplements are effective in raising serum 25-hydroxyvitamin d from low baseline levels in adults: A systematic review
Winzenberg, T. M., et al.	2010	Vitamin D supplementation for improving bone mineral density in children
Witham, M. D., et al.	2009	Effect of vitamin D on blood pressure: A systematic review and meta-analysis
Wu, L., et al.	2017	Effects of calcium plus Vitamin D supplementation on blood pressure: A systematic review and meta-analysis of randomized controlled trials
Wu, S. H., et al.	2010	Effects of vitamin D supplementation on blood pressure
Xu, C., et al.	2016	Evaluation of responses to vitamin D3 (cholecalciferol) in patients on dialysis: A systematic review and meta-analysis

Yang, N., et al.	2015	Effects of vitamin D supplementation during pregnancy on neonatal vitamin D and calcium concentrations: A systematic review and meta-analysis
Zittermann, A., et al.	2015	Effect of Vitamin D or activated Vitamin D on circulating 1,25-dihydroxyvitamin D concentrations: A systematic review and metaanalysis of randomized controlled trials
Zittermann, A., et al.	2014	Vitamin D supplementation, body weight and human serum 25-hydroxyvitamin D response: A systematic review
Zittermann, A., et al.	2011	The role of vitamin D in dyslipidemia and cardiovascular disease
Zuk, A., et al.	2016	Effect of Vitamin D3 Supplementation on Inflammatory Markers and Glycemic Measures among Overweight or Obese Adults: A Systematic Review of Randomized Controlled Trials.
<b>INCORRECT STUDY TYPE – CONFERENCE ABSTRACT, REVIEW PAPER, LETTER, EDITORIAL</b>		
Abegunde, A. T., et al.	2016	Preventive health measures in inflammatory bowel disease
Adachi, J. D., et al.	2005	In whom and how to prevent glucocorticoid-induced osteoporosis
Agarwal, R., et al.	2016	Con: Nutritional Vitamin D replacement in chronic kidney disease and end-stage renal disease
Al Mheid, I., et al.	2017	Vitamin D and Cardiovascular Disease: Controversy Unresolved
Alvarez, M. J. M., et al.	2007	Pharmacological treatment of osteoporosis for people over 70
Andreatta, W., et al.	2014	Evidence-based nutritional advice for patients affected by age-related macular degeneration
Annweiler, C., et al.	2010	Vitamin D and bone fracture mechanisms: What about the non-bone 'Defense'?
Annweiler, C., et al.	2010	Vitamin D and ageing: Neurological issues
Anonymous	2005	Fall prevention programmes in older people
Anonymous	2009	Vitamin D, at high doses, prevents fractures
Bacchetta, J., et al.	2013	The consequences of pediatric renal transplantation on bone metabolism and growth
Barchetta, I., et al.	2017	Vitamin D Supplementation and Non-Alcoholic Fatty Liver Disease: Present and Future
Beaudart, C., et al.	2013	The effects of vitamin D on skeletal muscle strength: A meta-analysis of randomized controlled trials
Beaudart, C., et al.	2013	Meta-analysis of randomized controlled trials assessing the effects of vitamin D supplementation on skeletal muscle strength
Beaudart, C., et al.	2014	The effects of vitamin d on skeletal muscle strength, muscle mass and muscle power: A meta-analysis of randomized controlled trials
Beveridge, L. A., et al.	2013	Vitamin D and the cardiovascular system
Bi, Wei Guang., et al.	2018	735: Vitamin D supplementation during pregnancy and offspring mortality and morbidity: a systematic review
Bidar, S. S., et al.	2012	The influence of vitamin d supplementation on mean changes in serum 25(OH)D: A meta-analysis
Bijlsma, J. W., et al.	2000	Supplementation of vitamin D plus calcium is effective in corticosteroid-induced osteoporosis management
Bischoff-Ferrari, H. A., et al.	2005	Extra-skeletal effects of vitamin D
Bischoff-Ferrari, H. A., et al.	2010	Contribution of vitamin D to fracture prevention
Bischoff-Ferrari, H. A., et al.	2010	Vitamin D: Update bone and muscle effects
Bischoff-Ferrari, H. A., et al.	2004	Review: Prophylactic use of vitamin D reduces falls in older persons
Bischoff-Ferrari, H. A., et al.	2006	Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: A 3-year randomized controlled trial
Bischoff-Ferrari, H., et al.	2010	A higher dose of vitamin d is required for hip and non-vertebral fracture prevention: A pooled participant-based meta-analysis of 11 double-blind RCTS
Bjelakovic, G., et al.	2008	Vitamin D supplementation for prevention of mortality in adults
Bjelakovic, G., et al.	2008	Vitamin D supplementation for prevention of cancer in adults
Bjelakovic, G., et al.	2005	High-dose antioxidants to prevent cancer: Hype or hoax?
Bjelakovic, G., et al.	2015	Vitamin D supplementation for chronic liver disease-a cochrane hepato-biliary group systematic review
Bone, et al.	2002	Glucocorticoid-induced osteoporosis: guidelines for prevention and treatment
Borghì, M. M., et al.	2005	Evaluation of stature development during childhood and adolescence in individuals with familial hypophosphatemic rickets
Brown, S., et al.	2007	A stronger case for calcium and vitamin D in fracture prevention
Burris, H. H., et al.	2014	Vitamin D and gestational diabetes mellitus

Cederholm, T., et al.	2005	Nutritional treatment of bone fracture
Chadban, S., et al.	2010	Nutritional interventions for the prevention of bone disease in kidney transplant recipients
Challem, J., et al.	2006	Medical journal watch: Context and applications
Chaney, A., et al.	2015	Primary care management of vitamin D deficiency and liver disease
Chawes, B. L., et al.	2017	Prenatal vitamin d supplementation reduces risk of asthma/recurrent wheeze in early childhood: A meta-analysis of two randomized controlled trials
Chen, S., et al.	2015	Vitamin D deficiency and essential hypertension
Cherniack, E. P., et al.	2008	Hypovitaminosis D: A stealthy epidemic that requires treatment
Chung, M., et al.	2012	Review: Vitamin D with calcium reduces fractures in adults
Cosenso-Martin, L. N., et al.	2011	Is there an association between vitamin D and hypertension?
Crandall, M., et al.	2016	Prevention of fall-related injuries in the elderly: An Eastern Association for the Surgery of Trauma practice management guideline
Curtis, J. R., et al.	2007	Prevention and treatment of glucocorticoid-induced osteoporosis
Daly, S., et al.	2016	Clinical Inquiries: Does vitamin D without calcium reduce fracture risk?
Danik, J. S., et al.	2012	Vitamin D and cardiovascular disease
Davidson, Z. E., et al.	2011	Serum 25 hydroxyvitamin D in patients treated with glucocorticosteroids: A systematic review with meta analysis
De Francisco, A. L., et al.	2004	Secondary hyperparathyroidism: review of the disease and its treatment
De-Regil, L. M., et al.	2016	Vitamin D supplementation for women during pregnancy
Dierkes, J., et al.	2014	Vitamin D and calcium supplementation and its influence on muscle strength and mobility in community-dwelling elderly: A systematic review and meta-analysis
Eid, A. J., et al.	2006	Metabolic and morphologic complications of HIV infection
Emberson, J. R., et al.	2011	Vitamin d and risk of cardiovascular and non-cardiovascular mortality: A prospective cohort study and meta-analysis
Epstein, S., et al.	2006	Update of current therapeutic options for the treatment of postmenopausal osteoporosis
Fairfield, K. M., et al.	2002	Vitamins for chronic disease prevention in adults: scientific review
Fernandez, H., et al.	2016	Vitamin D and bone health in adults with epilepsy (a systematic review)
Fiechtner, J. J., et al.	2003	Hip fracture prevention: Drug therapies and lifestyle modifications that can reduce risk
Fong, J., et al.	2012	Hypocalcemia: Updates in diagnosis and management for primary care. [French, English]
Ford, J. A., et al.	2012	Vitamin D Supplementation Prevents Cardiac Failure; MRC RECORD Trial Analysis, Systematic Review And Meta-analysis
Fosnight, S. M., et al.	2008	Vitamin D supplementation to prevent falls in the elderly: Evidence and practical considerations
Francis, R. M., et al.	2006	Calcium, vitamin D and involutional osteoporosis
Francis, R. M., et al.	2006	Calcium and vitamin D in the prevention of osteoporotic fractures
Frost, S., et al.	2013	Calcium plus vitamin D supplementation: A meta-analysis of risk and benefit
Fry, C. M., et al.	2015	Vitamin D and risk of CVD: a review of the evidence
Gennari, L., et al.	2006	Vitamin D and its metabolites in the pathogenesis and treatment of osteoporosis
Giammanco, M., et al.	2015	Vitamin D in cancer chemoprevention
Gillie, O., et al.	2006	Why sun protection advice to the UK public must be remedied quickly
Glade, M. J., et al.	2012	A 21st century evaluation of the safety of oral vitamin D
Gourlay, M., et al.	2007	Prevention and treatment strategies for glucocorticoid-induced osteoporotic fractures
Gowen, M., et al.	2000	Emerging therapies for osteoporosis
Graat-Verboom, L., et al.	2009	Current status of research on osteoporosis in COPD: a systematic review
Grenier, S., et al.	2007	Vitamin D: Two indications for the price of one?
Grieger, J. A., et al.	2015	A review of the impact of dietary intakes in human pregnancy on infant birth-weight
Grubler, M. R., et al.	2016	Vitamin d and cardiovascular mortality: An individual participant data meta-analysis with standardized 25-hydroxyvitamin D
Guerrieri-Gonzaga, A., et al.	2013	Vitamin D and overall mortality

Gunta, S. S., et al.	2013	The effect of vitamin D status on risk factors for cardiovascular disease
Gupta, G., et al.	2007	Treatment of postmenopausal osteoporosis
Gupta, M., et al.	2007	Current status of hormone replacement therapy in post menopausal women
Guyatt, G. H., et al.	2002	Summary of meta-analyses of therapies for postmenopausal osteoporosis and the relationship between bone density and fractures
Hagino, H., et al.	2013	Eldecalcitol: Newly developed active vitamin D3 analog for the treatment of osteoporosis
Hamdy, R. C., et al.	2005	Review of treatment modalities for postmenopausal osteoporosis
Handoll, H. H. G., et al.	2007	Moving towards evidence-based healthcare for musculoskeletal injuries: Featuring the work of the Cochrane Bone, Joint and Muscle Trauma Group
Handoll, H., et al.	2009	Update of a systematic review of vitamin D for preventing osteoporotic fractures
Hansen, L. B., et al.	2006	Osteoporosis update: Effective prevention and treatment
Hansen, L. B., et al.	2004	Prevention and treatment of nonpostmenopausal osteoporosis
Hauselmann, H. J., et al.	2003	A comprehensive review of treatments for postmenopausal osteoporosis
Heaney, R. P., et al.	2002	The importance of calcium intake for lifelong skeletal health
Heaney, R. P., et al.	2007	Bone health
Heaney, R. P., et al.	2013	All-source basal vitamin D inputs are greater than previously thought and cutaneous inputs are smaller
Hilario, A. M. A., et al.	2016	Maternal vitamin D supplementation among lactating mothers in the prevention of vitamin D deficiency among breastfed term infants: A meta analysis
Hochberg, M., et al.	2000	Preventing fractures in postmenopausal women with osteoporosis: A review of recent controlled trials of antiresorptive agents
Hosking, D. J., et al.	2005	Osteoporosis therapy: An example of putting evidence-based medicine into clinical practice
Hudson, J. Q., et al.	2006	Secondary hyperparathyroidism in chronic kidney disease: Focus on clinical consequences and vitamin D therapies
Huttemann, D., et al.	2017	Meta-analysis: Vitamin D for protection against colds
Hypponen, E., et al.	2012	Vitamin D and pre-eclampsia: A systematic review and meta-analysis
Ioachimescu, A., et al.	2007	Etidronate: What is its place in treatment of primary osteoporosis and other demineralizing diseases today?
Ioannou, C., et al.	2015	Maternal vitamin D deficiency and fetal growth
Iwamoto, J., et al.	2007	Effects of antifracture drugs in postmenopausal, male and glucocorticoid-induced osteoporosis - usefulness of alendronate and risedronate
Jian, Luo, et al.	2016	Can Vitamin D Supplementation in Addition to Asthma Controllers Decrease Asthmatic Exacerbations in Patients With Asthma? A Meta-analysis
Karwowski, W., et al.	2012	The mechanism of vascular calcification - a systematic review
Katz, S., et al.	2004	Osteoporosis in patients with inflammatory bowel disease: Risk factors, prevention, and treatment
Kearns, M. D., et al.	2015	Impact of Vitamin D on Infectious Disease: A Systematic Review of Controlled Trials
Knight, C. L., et al.	2006	Update in General Internal Medicine
Krabbe, C., et al.	2015	The effect of vitamin D on atopic dermatitis-a systematic review
Lakshmi, V. V., et al.	2017	A systematic review on diagnosis and management of postmenopausal osteoporosis
Lamberg-Allardt, C., et al.	2013	Vitamin D - a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations
Lambrinoudaki, I., et al.	2000	Management of steroid-induced osteoporosis
Langlois, P. L., et al.	2017	Vitamin D supplementation in the critically ill: Systematic review and meta-analysis
Lees, C. M., et al.	2000	The current management of cystic fibrosis
Lerchbaum, E., et al.	2012	Mechanisms in endocrinology - Vitamin D and fertility: A systematic review
Lewis, J., et al.	2013	The cardiovascular safety of calcium supplementation with or without vitamin D in elderly women: A collaborative meta-analysis of published and unpublished trial level evidence from randomised controlled trials
Lichtenstein, G. R., et al.	2003	Evaluation of Bone Mineral Density in Inflammatory Bowel Disease: Current Safety Focus
Lilliu, H., et al.	2003	Calcium-vitamin D-3 supplementation is cost-effective in hip fractures prevention
Locatelli, F., et al.	2008	New approaches to treatment of secondary hyperparathyroidism
Loney, Kerri, et al.	2013	Vitamin D Supplementation Recommendations for Post Roux-en-Y Gastric Bypass Patients: A Systematic Literature Review



MacDonald, H. M., et al.	2012	Comparison of vitamin D(2) and vitamin D(3) supplementation in increasing serum 25-hydroxyvitamin D status: a systematic review and meta-analysis
Maglione, M., et al.	2007	Effectiveness and safety of vitamin D in relation to bone health
Mann, M. C., et al.	2014	Vitamin d analogues, mortality, and cardiovascular risk in chronic kidney disease: A systematic review and meta-analysis of randomized controlled trials
Martineau, A. R., et al.	2016	Vitamin D for the management of asthma: Cochrane systematic review and meta-analysis
Mengarelli, C., et al.	2015	Vitamin D supplementation to prevent acute respiratory infection: individual patient data meta-analysis of randomised controlled trials
Meunier, P. J., et al.	1999	Evidence-based medicine and osteoporosis: a comparison of fracture risk reduction data from osteoporosis randomised clinical trials
Mihailescu, V., et al.	2004	Evolving approaches to management of osteoarthritis
Mikropoulos, Ch., et al.	2004	Colorectal cancer and chemoprevention
Moran, D. S., et al.	2013	Vitamin d and physical performance
Muir, S. W., et al.	2011	The efficacy of vitamin D supplementation on muscle, gait and balance in older adults. A systematic review and meta-analysis of the role of doses and regimens
Namaka, M., et al.	2008	Examining the evidence: Complementary adjunctive therapies for multiple sclerosis
Nehra, D., et al.	2013	A.S.P.E.N. clinical guidelines: nutrition support of neonatal patients at risk for metabolic bone disease
No authors listed	2010	New meta-analysis on vitamin D, calcium and fractures
No authors listed	2012	Vitamin D supplementation and risk of fractures, falls, and bone loss
No authors listed	2013	[Meta analysis. Vitamin D alone does not prevent osteoporosis]
No authors listed	2018	Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis
Oliver, D., et al.	2007	Strategies to prevent falls and fractures in hospitals and care homes and effect of cognitive impairment: Systematic review and meta-analyses
Oliver, D., et al.	2010	Preventing falls and fall-related injuries in Hospitals
O'Malley, P. A., et al.	2015	Prescribing Sunshine: Evidence for Vitamin D Supplements
Patel, V. B., et al.	2012	Calcium affects on vascular endpoints
Pereira, R. M., et al.	2012	Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis
Perez-Lopez, F. R.	2004	Postmenopausal osteoporosis and alendronate
Pericleous, M., et al.	2014	Nutrition and pancreatic cancer
Pfortmueller, C. A., et al.	2014	Reducing fall risk in the elderly: Risk factors and fall prevention, a systematic review
Pham, A. N., et al.	2009	Osteoporosis in older women
Pharande, P., et al.	2015	Vitamin D supplementation for prevention of vitamin D deficiency in preterm and low birth weight infants
Pilz, S., et al.	2010	Role of vitamin D in arterial hypertension
Pilz, S., et al.	2011	Vitamin D, cardiovascular disease and mortality
Pilz, S., et al.	2018	The role of vitamin D in fertility and during pregnancy and lactation: A review of clinical data
Poole, K. E. S., et al.	2006	Osteoporosis and its management
Popp, A. W., et al.	2006	Glucocorticosteroid-induced spinal osteoporosis: Scientific update on pathophysiology and treatment
Qureshi, N. A., et al.	2013	Mood disorders and complementary and alternative medicine: a literature review
Rabenda, V., et al.	2010	Relationship between bone mineral density changes and risk of nonvertebral fractures among women receiving calcium with or without vitamin D supplementation: A meta-analysis
Reginster, J. Y., et al.	2005	Importance of alfacalcidol in clinical conditions characterized by high rate of bone loss
Reid, I. R., et al.	2011	Cardiovascular effects of calcium supplementation
Reid, I. R., et al.	2008	Effect of calcium supplementation on hip fractures
Reid, I. R., et al.	2015	Effects of vitamin D supplements on bone density
Reshef, R., et al.	2002	The chronic cholestasis enigma in adults
Reviews, N. H., et al.	1996	Preventing falls and subsequent injury in older people
Riazv, H., et al.	2013	Vitamin D as a supplementary agent in the treatment of pulmonary tuberculosis: A systematic review and meta-analysis of randomized controlled trials

Sacks, Henry S.	2017	2017 - Review: In children and adults, vitamin D3 supplementation reduces risk for acute respiratory tract infection
Saldanha, I. J., et al.	2011	Use of hydroxylated vitamin D supplements in cystic fibrosis: Results of a systematic review
Savage, J., et al.	2011	Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis
Schmid, H., et al.	2010	Pharmacotherapy of end-stage renal disease
Scragg, R., et al.	2018	Emerging Evidence of Thresholds for Beneficial Effects from Vitamin D Supplementation
Soares, M. J., et al.	2011	Calcium and vitamin D for obesity: a review of randomized controlled trials
Stott, D. J., et al.	2000	Systematic reviews
Tamura, Y., et al.	2004	Glucocorticoid-induced osteoporosis
The Swedish Council on Technology Assessment in Health, Care	2006	Treatment with vitamin D and calcium
Tian, S., et al.	2016	Efficacy of vitamin D supplement in patients with IBD: A systematic review and meta-analysis
van den Bergh, J. P., et al.	2011	Optimal use of vitamin D when treating osteoporosis
Varenna, M., et al.	2013	Safety profile of drugs used in the treatment of osteoporosis: A systematic review of the literature
Veninšek, G., et al.	2018	Management of Frailty at Individual Level - Clinical Management: Systematic Literature Review
Vieira, E. R., et al.	2016	Prevention of falls in older people living in the community
Villar, L. M., et al.	2012	Vitamin D supplementation influences sustained virological response rate in Hepatitis C: A systematic review and meta-analysis
Von Tirpitz, C., et al.	2003	Management of osteoporosis in patients with gastrointestinal diseases
Weinberger, T., et al.	2018	Prenatal intake of vitamins and allergic outcomes in the offspring: A systematic review and meta-analysis
Weng, H., et al.	2017	Randomised trials of vitamin D3 for critically ill patients in adults: systematic review and meta-analysis with trial sequential analysis
Winzenberg T. M., et al.	2013	Vitamin D supplementation in infancy for improving bone density
Winzenberg, T. M., et al.	2011	Vitamin D supplementation for improving bone mineral density in children
Xu, L., et al.	2012	Vitamin D supplementation on albuminuria and progression of pre-dialysis diabetic nephropathy and other kidney diseases: A meta analysis and systematic review of randomized controlled trials
Youssef, D., et al.	2012	Differences in outcomes between cholecalciferol and ergocalciferol supplementation in veterans with inflammatory bowel disease
Zittermann, A., et al.	2017	The Biphasic Effect of Vitamin D on the Musculoskeletal and Cardiovascular System
<b>INCORRECT STUDY TYPE – ECONOMICS</b>		
Aguiar, M., et al.	2017	Preventing vitamin D deficiency (VDD): a systematic review of economic evaluations
Brezinski, E. A., et al.	2015	Economic burden of psoriasis in the United States a systematic review
Church, J. L., et al.	2015	Cost Effectiveness of Falls and Injury Prevention Strategies for Older Adults Living in Residential Aged Care Facilities
Hagen, G., et al.	2016	The predicted lifetime costs and health consequences of calcium and vitamin D supplementation for fracture prevention-the impact of cardiovascular effects
Hamilton, M. P., et al.	2015	Psoriasis treatment and management - A systematic review of full economic evaluations
Lorenzoni, V., et al.	2015	The cost-effectiveness of drug therapies to treat secondary hyperparathyroidism in renal failure: A focus on evidence regarding paricalcitol and cinacalcet
Nuijten, M., et al.	2009	Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: a US perspective
Pacis, M. M., et al.	2015	Vitamin D and assisted reproduction: should vitamin D be routinely screened and repleted prior to ART? A systematic review
Poole, C. D., et al.	2014	The short-term impact of vitamin D-based hip fracture prevention in older adults in the United Kingdom
Ruwanpathirana, T., et al.	2015	Can oral vitamin D prevent the cardiovascular diseases among migrants in Australia? Provider perspective using Markov modelling
<b>OTHER (E.G. DUPLICATE, OLD VERSION OF AN INCLUDED UPDATE)</b>		
Avenell, A., et al.	2014	Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men
Akbari, M., et al.	2017	The Effects of Vitamin D Supplementation on Glucose Metabolism and Lipid Profiles in Patients with Gestational Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Andersen, R., et al.	2016	New treatment strategies for hidradenitis suppurativa

Anonymous	2004	Meta-analysis shows vitamin D reduces falls
Anonymous	2005	Vitamin D analogs appear superior to native form in preventing bone loss, fractures
Anonymous	2005	Vitamin supplements
Anonymous	2006	1000 mg calcium and 400 IU vitamin D not very effective for fracture prevention
Anonymous	2007	Limited effect of calcium and vitamin D in reducing osteoporotic fractures
Anonymous	2008	The benefits of osteoporosis drugs
Autier, P., et al.	2017	Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials
Autier, P., et al.	2017	Effect of vitamin D supplementation on non-skeletal disorders: a systematic review of meta-analyses and randomised trials
Avenell, A., et al.	2009	Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis
Avenell, A., et al.	2005	Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis
Bacchetta, J., et al.	2008	Long-term steroid therapy in children: Is adjunct therapy relevant in nephrotic syndrome?. [French]
Balzer, K., et al.	2012	Falls prevention for the elderly
Barro-Belaygues, N.	2010	Prevention of nonvertebral fractures with oral vitamin D and dose dependency a meta-analysis of randomized controlled trials
Beaudart, C., et al.	2014	The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials
Becker, C. B., et al.	2008	Does supplementation with calcium alone or in combination with vitamin D reduce the risk of osteoporotic fracture?
Beckwee, D., et al.	2018	Pharmacological Interventions to Improve Muscle Mass, Muscle Strength and Physical Performance in Older People: An Umbrella Review of Systematic Reviews and Meta-analyses
Benitez-Rosario, M. A., et al.	2010	An objective meta analysis of the decrease of the incidence of nonvertebral and hip fractures in elderly persons with the administration of vitamin D
Bischoff-Ferrari, H. A., et al.	2006	Vitamin D and muscle function
Bischoff-Ferrari, H. A., et al.	2012	A pooled analysis of vitamin D dose requirements for fracture prevention
Bjelakovic, G., et al.	2011	Vitamin D supplementation for prevention of mortality in adults
Butler, M., et al.	2018	Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review
Cameron, I. D., et al.	2012	Interventions for preventing falls in older people in care facilities and hospitals
Cameron, I. D., et al.	2010	Interventions for preventing falls in older people in nursing care facilities and hospitals
Cheng, P., et al.	2018	Serum 25-hydroxyvitamin D and risk of type 2 diabetes in older adults: A dose-response meta-analysis of prospective cohort studies: Retraction
Cheng, P., et al.	2018	Retracted: Serum 25-hydroxyvitamin D and risk of type 2 diabetes in older adults: A dose-response meta-analysis of prospective cohort studies
Chien-Ming, C., et al.	2017	EFFECTS OF VITAMIN D SUPPLEMENTATION ON MUSCLE STRENGTH IN ATHLETES: A SYSTEMATIC REVIEW
Christenson, E. S., et al.	2012	Osteoporosis management in post-menopausal women
Chung, M., et al.	2009	Vitamin D and calcium: a systematic review of health outcomes
Cranney, A., et al.	2002	IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis
Dix, C. F., et al.	2017	A Systematic Review: Vitamin D Status and Sleeve Gastrectomy
Ferguson, J. H., et al.	2009	Vitamin D supplementation for cystic fibrosis
Gao, X. R., et al.	2017	The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials
Geary Denis, F., et al.	2010	Interventions for bone disease in children with chronic kidney disease
Gillespie, L. D., et al.	2003	Interventions for preventing falls in elderly people
Gillespie, W.J., et al.	2001	Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis
Gillespie, W.J., et al.	2000	Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis
Gomes, F. M., et al.	2013	Vitamin D - A multiple sclerosis' promise
Goran, B., et al.	2014	Vitamin D supplementation for prevention of cancer in adults
Gupta, G., et al.	2009	Vitamin D supplementation and chronic kidney disease
Hagenfeldt, K., et al.	2003	Osteoporosis - prevention, diagnosis and treatment

He, S., et al.	2018	Effect of vitamin D supplementation on fasting plasma glucose, insulin resistance and prevention of type 2 diabetes mellitus in non-diabetics: A systematic review and meta-analysis
Hempel, S., et al.	2017	A systematic review of the effects of modifiable risk factor interventions on the progression of multiple sclerosis
Homik, J., et al.	2000	Calcium and vitamin D for corticosteroid-induced osteoporosis
Hyppönen, E., et al.	2013	Vitamin D and pre-eclampsia: Original data, systematic review and meta-analysis
Hyppönen, E., et al.	2014	Vitamin D and pre-eclampsia: original data, systematic review and meta-analysis
Kalli, E. G., et al.	2017	Association of nutrients with biomarkers of Alzheimer's disease
Khaing, W., et al.	2017	Calcium and Vitamin D Supplementation for Prevention of Preeclampsia: A Systematic Review and Network Meta-Analysis
Li, Z. N., et al.	2006	Influencing factors of mandible osteoporosis
Lozano-Ortega, G., et al.	2018	Effects of calcimimetics on long-term outcomes in dialysis patients: Literature review and Bayesian meta-analysis
Malihi, Z., et al.	2017	Noncalcemic adverse effects and withdrawals in randomized controlled trials of long-term vitamin D2 or D3 supplementation: a systematic review and meta-analysis
Malihi, Z., et al.	2016	Hypercalcemia, hypercalciuria, and kidney stones in long-term studies of vitamin D supplementation: a systematic review and meta-analysis
Mazzaferro, S., et al.	2007	[Calcimimetics, phosphate binders, vitamin D and its analogues for treating secondary hyperparathyroidism in chronic kidney disease: guideline from the Italian Society of Nephrology]
Medley, N., et al.	2018	Interventions during pregnancy to prevent preterm birth: An overview of Cochrane systematic reviews
Mello, R. G., et al.	2010	Vitamin D and prevention of falls in the elderly: a systematic review
Meriardi, M., et al.	2003	Nutritional interventions during pregnancy for the prevention or treatment of impaired fetal growth: An overview of randomized controlled trials
Mosekilde, L., et al.	2007	Fracture prevention in postmenopausal women
Palmer, S. C., et al.	2005	Interventions for preventing bone disease in kidney transplant recipients: A systematic review of randomized controlled trials
Palmer, S. C., et al.	2015	Association of drug effects on serum parathyroid hormone, phosphorus, and calcium levels with mortality in CKD: A meta-analysis
Plawecki, K., et al.	2010	Bone health nutrition issues in aging
Pojsupap, S., et al.	2014	Efficacy of high-dose vitamin D in pediatric asthma: a systematic review and meta-analysis, Screening for vitamin D deficiency: systematic review for the U.S. Preventive Services Task Force Recommendation
Rejnmark, L., et al.	2011	Effects of vitamin D on muscle function and performance: A review of evidence from randomized controlled trials
Rogovik, A. L., et al.	2010	Safety considerations and potential interactions of vitamins: Should vitamins be considered drugs?
Rutjes, A. W., et al.	2018	Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life
Ryan, L. M., et al.	2011	Vitamin D supplementation of deficient children may improve bone mineral density
Scheel, F., et al.	2016	[Is vitamin D supplementation effective for the prevention of falls in elderly people?]
Shab-Bidar, S., et al.	2014	Serum 25(OH)D response to vitamin D3 supplementation: a meta-regression analysis
Sherzai, A. Z., et al.	2016	Micronutrients and Risk of Parkinson's Disease: A Systematic Review
Slee, P. H. Th J.	2010	Fall prevention with vitamin D supplementation: A meta-analysis of randomized trials
Stein, E. M., et al.	2011	Prevention of fractures after solid organ transplantation: A meta-analysis
Straube, S., et al.	2010	Vitamin D for the treatment of chronic painful conditions in adults
Suzuki, T., et al.	2017	[Update on recent progress in vitamin D research. Eldecalcitol<sup>R</sup> and Fall Prevention.]
Swedish Council on Health Technology, Assessment	2003	Osteoporosis – Prevention, Diagnosis and Treatment: A Systematic Review
Theodoratou, E., et al.	2014	Vitamin D and multiple health outcomes: umbrella review of systematic reviews and meta-analyses of observational studies and randomised trials
Thomas, G. N., et al.	2012	Hyperglycaemia and vitamin D: a systematic overview
Urrutia, R. P., et al.	2012	Vitamin D in pregnancy: Current concepts. []
Vaishya, R., et al.	2018	Does vitamin D deficiency influence the incidence and progression of knee osteoarthritis? - A literature review
Vásquez-Morales, A., et al.	2013	[Exercise and nutritional supplements; effects of combined use in people over 65 years; a systematic review]

Vlaeyen, E., et al.	2015	Characteristics and effectiveness of fall prevention programs in nursing homes: A systematic review and meta-analysis of randomized controlled trials
Wallace, T., et al.	2015	Calcium plus vitamin D supplementation and risk of fractures: An updated meta-analysis from NOF
Weaver, C. M., et al.	2016	Calcium plus vitamin D supplementation and risk of fractures: An updated meta-analysis from the National Osteoporosis Foundation.[Erratum appears in Osteoporos Int. 2016 Aug;27(8):2643-6; PMID: 27401092]
Wu, H., et al.	2017	Einfluss der Vitamin-D- und Kalziumsupplementierung auf Stürze bei älteren Erwachsenen : Eine systematische Übersicht und Metaanalyse, The effect of vitamin D and calcium supplementation on falls in older adults : A systematic review and meta-analysis
Xiao, Y., et al.	2010	Systematic review on vitamin D prevent and treat bone loss in renal-transplant patients
Yamshchikov, A. V., et al.	2009	Vitamin D for treatment and prevention of infectious diseases: A systematic review of randomized controlled trials
Zhang, N., et al.	2013	Effects of vitamin D supplement on blood pressure: A systematic review
<b>EXCLUDED AS ALTHOUGH THE STUDY ADDRESSES A RELEVANT OUTCOME FOR A RISK GROUP WE ARE CONSIDERING, AN ALTERNATIVE UMBRELLA REVIEW/COCHRANE REVIEW/MORE RECENT SYSTEMATIC REVIEW IS AVAILABLE FOR THE OUTCOME-RISK GROUP PAIR</b>		
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
Geddes, J. A., et al.	2013	Evidence for the treatment of osteoporosis with vitamin D in residential care and in the community dwelling elderly
Hamdy, R. C., et al.	2008	Calcium intake and hip fracture risk in men and women: A meta-analysis of prospective cohort studies and randomized controlled trials
. Kanis, J. A., et al.	2007	Glucocorticoid-induced osteoporosis: A systematic review and cost-utility analysis
Amin, S., et al.	1999	The role of vitamin D in corticosteroid-induced osteoporosis: a meta-analytic approach
Annweiler, C., et al.	2009	Vitamin D-related changes in physical performance: A systematic review
Autier, P., et al.	2014	Vitamin D status and ill health: A systematic review
Autier, P., et al.	2007	Vitamin D supplementation and total mortality: A meta-analysis of randomized controlled trials
Avenell, A., et al.	2014	Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men
B. J. Gates, B. J., et al.	2009	Review of osteoporosis pharmacotherapy for geriatric patients
Barnard, K., et al.	2010	Extraskeletal effects of vitamin D in older adults: Cardiovascular disease, mortality, mood, and cognition
Beaudart, C., et al.	2014	The effects of vitamin d on skeletal muscle strength, muscle mass, and muscle power: A systematic review and meta-analysis of randomized controlled trials
Bergman, G. J. D., et al.	2010	Efficacy of vitamin D<sup>3</sup> supplementation in preventing fractures in elderly women: A meta-analysis
Bi, W. G., et al.	2018	Association between Vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: A systematic review and 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
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
Bischoff-Ferrari, H. A., et al.	2005	Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials
Bischoff-Ferrari, H. A., et al.	2012	A pooled analysis of vitamin D dose requirements for fracture prevention.[Erratum appears in N Engl J Med. 2012 Aug 2;367(5):481 Note: Oray, Endel J [corrected to Orav, Endel J]]
Bischoff-Ferrari, H. A., et al.	2004	Effect of Vitamin D on Falls: A Meta-analysis
Bjelakovic, G., et al.	2014	Vitamin D supplementation for prevention of cancer in adults
Bolland, M. J., et al.	2015	Calcium intake and risk of fracture: Systematic review
Bolland, M. J., et al.	2014	The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: A trial sequential meta-analysis
Bolland, M. J., et al.	2014	Vitamin D supplementation and falls: A trial sequential meta-analysis
Cameron, I. D., et al.	2018	Interventions for preventing falls in older people in care facilities and hospitals
Cesareo, R., et al.	2015	Effectiveness and safety of calcium and vitamin D treatment for postmenopausal osteoporosis
Christesen, H. T., et al.	2012	The impact of vitamin D on pregnancy: A systematic review
Christesen, H. T., et al.	2012	The impact of vitamin D in pregnancy on extraskeletal health in children: A systematic review
Chua, G. T., et al.	2011	Association Between Vitamin D Dosing Regimen and Fall Prevention in Long-term Care Seniors

Chung, M., et al.	2016	Calcium intake and cardiovascular disease risk: An updated systematic review and meta-analysis
Chung, M., et al.	2011	Vitamin D with or without calcium supplementation for prevention of cancer and fractures: An updated meta-analysis for the U.S. preventive services task force
Cooper, K., et al.	2010	Chemoprevention of colorectal cancer: systematic review and economic evaluation
Cranney, A., et al.	2008	Summary of evidence-based review on vitamin D efficacy and safety in relation to bone health
D. Group	2010	Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe
De Nijs, R. N. J., et al.	2004	Prevention and treatment of glucocorticoid-induced osteoporosis with active vitamin D<sup>3</sup> analogues: A review with meta-analysis of randomized controlled trials including organ transplantation studies
De-Regil, L. M., et al.	2012	Vitamin D supplementation for women during pregnancy
Dewansingh, P., et al.	2018	Supplemental protein from dairy products increases body weight and vitamin D improves physical performance in older adults: a systematic review and meta-analysis
Diao, Yang, N., et al.	2017	Effect of vitamin D supplementation on knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials
Elamin, M. B., et al.	2011	Vitamin D and cardiovascular outcomes: A systematic review and meta-analysis
Gao, X. R., et al.	2017	The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials
Gillespie, L. D., et al.	2012	Interventions for preventing falls in older people living in the community
Goran, B., et al.	2014	Vitamin D supplementation for prevention of mortality in adults
Gradel, L., et al.	2016	Screening and Treatment of Vitamin D Deficiency on Hospital Admission: Is There a Benefit for Medical Inpatients?
Guirguis-Blake, J. M., et al.	2018	Interventions to prevent falls in older adults: Updated evidence report and systematic review for the US Preventive Services Task Force
Guirguis-Blake, J. M., et al.	2018	Interventions to Prevent Falls in Community-Dwelling Older Adults: A Systematic Review for the U.S. Preventive Services Task Force
Guo, J. L., et al.	2014	Interventions to reduce the number of falls among older adults with/without cognitive impairment: An exploratory meta-analysis
Hofmeyr, G. J., et al.	2014	Low-dose calcium supplementation for preventing pre-eclampsia: A systematic review and commentary
Hussain, S., et al.	2017	Vitamin D supplementation for the management of knee osteoarthritis: a systematic review of randomized controlled trials
Hypponen, E., et al.	2014	Vitamin D and Pre-Eclampsia: Original data, systematic review and meta-analysis
Jackson, C., et al.	2007	The effect of cholecalciferol (vitamin D<sup>3</sup>) on the risk of fall and fracture: A meta-analysis
Jolliffe, D. A., et al.	2019	Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials
Kahwati, L. C., et al.	2018	Vitamin D, calcium, OR combined supplementation for the primary prevention of fractures in community-dwelling adults evidence report and systematic review for the US Preventive Services Task Force
Kalyani, R. R., et al.	2010	Vitamin D treatment for the prevention of falls in older adults: Systematic review and meta-analysis
Kamudoni, P., et al.	2016	An estimate of the economic burden of vitamin D deficiency in pregnant women in the United Kingdom
Kanis, J. A., et al.	2002	Treatment of established osteoporosis: a systematic review and cost-utility analysis
Keum, N., et al.	2014	Vitamin D supplements and cancer incidence and mortality: A meta-analysis
Lai, J. K., et al.	2010	Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies
LeBlanc, E. S., et al.	2015	Screening for vitamin d deficiency: A systematic review for the U.S. Preventive services task force
Lesley, D. G., et al.	2012	Interventions for preventing falls in older people living in the community
Lewis, J. R., et al.	2015	The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: A collaborative meta-Analysis of randomized controlled trials
Li, G., et al.	2014	Efficacy of vitamin D supplementation in depression in adults: A systematic review
Lister, T., et al.	2008	Should long-term care residents be supplemented with vitamin D?
Mao, P. J., et al.	2013	Effect of calcium or vitamin D supplementation on vascular outcomes: A meta-analysis of randomized controlled trials
Marcus, R., et al.	2002	Antiresorptive treatment of postmenopausal osteoporosis: Comparison of study designs and outcomes in large clinical trials with fracture as an endpoint
Martineau, A. R., et al.	2017	Vitamin D supplementation to prevent acute respiratory tract infections: Systematic review and meta-analysis of individual participant data

Michael, Y. L., et al.	2010	Primary care-relevant interventions to prevent falling in older adults: A systematic evidence review for the U.S. Preventive Services Task Force
Michael, Y. L., et al.	2010	Interventions to Prevent Falls in Older Adults: An Updated Systematic Review
Morgan, A.J., et al.	2008	Self-help interventions for depressive disorders and depressive symptoms: A systematic review
Muir, S. W., et al.	2011	Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: A systematic review and meta-analysis
Murad, M. H., et al.	2012	Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis
Murad, M. H., et al.	2011	The effect of vitamin D on falls: A systematic review and meta-analysis
Nakamura, K., et al.	2006	Efficacy of optimization of vitamin D in preventing osteoporosis and osteoporotic fractures: A systematic review
Newberry, S. J., et al.	2014	Vitamin D and calcium: a systematic review of health outcomes (update)
Neyens, J. C., et al.	2011	Effectiveness and Implementation Aspects of Interventions for Preventing Falls in Elderly People in Long-Term Care Facilities: A Systematic Review of RCTs
O'Callaghan, K. M., et al.	2018	Systematic review of vitamin D and hypertensive disorders of pregnancy
O'Donnell, S., et al.	2008	Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls
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
Perez-Lopez, F. R., et al.	2015	Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: A systematic review and meta-analysis of randomized controlled trials
Phang, J. K., et al.	2018	Complementary and alternative medicine for rheumatic diseases: A systematic review of randomized controlled trials
Purwani, J. M., et al.	2017	The role of vitamin D in pre-eclampsia: A systematic review
Rejmark, L., et al.	2012	Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials
Richy, F., et al.	2008	Differential effects of D-hormone analogs and native vitamin D on the risk of falls: A comparative meta-analysis
Rosendahl-Riise, H., et al.	2017	Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis
Rutjes, A. W. S., et al.	2018	Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life
Sperati, F., et al.	2013	Vitamin D Supplementation and Breast Cancer Prevention: A Systematic Review and Meta-Analysis of Randomized Clinical Trials
Stern, C., et al.	2009	Interventions to reduce the incidence of falls in older adult patients in acute-care hospitals: a systematic review
Stockton, K. A., et al.	2011	Effect of vitamin D supplementation on muscle strength: A systematic review and meta-analysis
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
Thorne-Lyman, A., et al.	2012	Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: A systematic review and meta-analysis
Tricco, A. C., et al.	2017	Comparisons of interventions for preventing falls in older adults: A systematic review and meta-analysis
Vahdaninia, M., et al.	2017	Prenatal Intake of Vitamins and Allergic Outcomes in the Offspring: A Systematic Review and Meta-Analysis
Wang, L., et al.	2010	Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events
Weaver, C. M., et al.	2016	Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation
Weaver, C. M., et al.	2016	Erratum and additional analyses re: Calcium plus vitamin D supplementation and the risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation
Wu, H., et al.	2017	The effect of vitamin D and calcium supplementation on falls in older adults : A systematic review and meta-analysis
Zhang, Q., et al.	2016	Effect of Vitamin D receptor activators on glomerular filtration rate: A meta-analysis and systematic review
Zhao, J. G., et al.	2017	Association between calcium or Vitamin D supplementation and fracture incidence in community-dwelling older adults a systematic review and meta-analysis