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Comité voor de evalutie van de medische praktijk inzake geneesmiddelen

RATIONAL USE OF CALCIUM AND VITAMIN D

Systematic literature review :
full report

Consensus conference
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ABBREVIATIONS

1, 25$(OH)_2$ D = 1, 25-dihydroxyvitamin D
25(OH)D = 25-hydroxy-vitamin D
BMD = bone mineral density
C = controlled
Ca = calcium
CBO = Centraal BegeleidingsOrgaan voor intercollegiale toetsing
CEBAM = Centre for Evidence Based Medicine
CHD = coronary heart disease
CI = confidence interval
CV= cardiovascular
DB = Double blind
HGR = Hoge Gezondheidsraad
HR = hazard ratio
HRT = Hormone replacement therapy
ICSI = Institute for Clinical Systems Improvement
IOM = Institute of Medicine
ITT = intention to treat analysis
MA = meta-analysis
MI = Myocardial infarction
MC = Multiple center
n = number of patients
NA = not applicable
NICE =National Institute for Health and Care Excellence
NS= non statistically significant
OR = odds ratio
PL = placebo
PTH= parathyroid hormone
PTS = patients
RCT = Randomized controlled trial
RR = relative risk
SC = single centre
SD = standard deviation
SERM = selective oestrogen receptor modulator
SS = statistically significant
USPSTF = U.S. Preventive Service Task Force
Vit = vitamin

1. Methodology

1.1 Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference "Vitamin D and Calcium" which will take place on 28 may 2015.

1.1.1 Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

1. Prévention de l'ostéoporose et des fractures de fragilité

1. Preventie van osteoporose en broosheidsfracturen

1.1. Vitamine D (25OH D)

1.1. Vitamine D (25OH D)

1.1.1 Dosage sanguin

-1.1.1*Dosering in het bloed*

Question 1 / Vraag 1

Quelles sont les normes et les méthodes de dosage correctes ?

Welke zijn de referentiewaarden en welk is de standaard gehaltebepaling (dosering)?

Question 2 / Vraag 2

Chez quels patients un premier dosage sanguin de la vitamine D est-il indiqué ?

Bij welke patiënten is een eerste gehaltebepaling van vitamine D in het bloed aangewezen?

Question 3 / Vraag 3

Une répétition des dosages de la vitamine D est-elle justifiée et dans quelles circonstances ?

Zijn nieuwe gehaltebepalingen van vitamine D verantwoord en in welke omstandigheden?

1.1.2 Administration de suppléments de vitamine D

1.1.2 *Toediening van vitamine-D-supplementen*

Question 4 / Vraag 4

Quelles sont les indications validées d'administration de suppléments de vitamine D chez un adulte ?

Welke zijn de gevalideerde indicaties voor toediening van vitamine-D-supplementen bij volwassenen?

Question 5 / Vraag 5

Un dosage sanguin de la vitamine D est-il nécessaire avant l'administration de suppléments de vitamine D ?

Is er een gehaltebepaling van vitamine D in het bloed nodig vóór toediening van vitamine-D-supplementen?

Question 6 / Vraag 6
Quelles sont les doses de suppléments de vitamine D à recommander ?
Welke zijn aan te raden dosissen vitamine-D-supplementen?

1.2. Calcium
1.2. Calcium

Question 7 / Vraag 7
Quelles sont les doses de suppléments calciques à administrer en complément à l'administration de suppléments de vitamine D et cet apport de suppléments calciques doit-il être adapté à l'apport alimentaire de calcium évalué à l'anamnèse ?
In welke dosis wordt calciumsupplement toegediend als aanvulling van vitamine-D-supplementen en moet die dosis calcium worden aangepast aan de dosis calcium die via de voeding wordt opgenomen en die naar voren komt uit de anamnese?

2. Traitement de l'ostéoporose
2. Behandeling van osteoporose

Question 8 / Vraag 8
Des suppléments de vitamine D et de calcium doivent-ils toujours être administrés en complément d'un traitement (bisphosphonates ou autres) d'une ostéoporose ?
Moeten vitamine-D- en calciumsupplementen altijd worden toegediend als aanvulling op een osteoporosebehandeling met geneesmiddelen (bisfosfonaten of andere)?

Question 9 / Vraag 9
L'apport de suppléments calciques doit-il être adapté à l'apport alimentaire de calcium évalué à l'anamnèse ?
Moet de dosis calciumsupplement aangepast worden aan de dosis calcium die via de voeding wordt opgenomen en die naar voren komt uit de anamnese?

Question 10 / Vraag 10
Un dosage initial de la vitamine D et une répétition des dosages de la vitamine D sont-ils justifiés ?
Bestaat er evidentie voor een eerste gehaltebepaling van vitamine D en moet die later herhaald worden?

3. Prévention des chutes chez la personne âgée
3. Valpreventie bij ouderen

Question 11 / Vraag 11
L'apport de suppléments de vitamine D et de calcium est-il à recommander en prévention des chutes chez la personne âgée et si oui :
- avec un dosage préalable de la vitamine D ?
- à quelles doses ?
- avec quelle surveillance ?

Kan de toediening van vitamine-D- en calciumsupplementen aangeraden worden in het kader van

valpreventie bij ouderen en zo ja:
met een voorafgaande gehaltebepaling van vitamine D?
in welke dosissen?
onder welke voorwaarden?

4. Sécurité de l'administration de suppléments calciques
4. Veilige toediening van calciumsupplementen

Question 12 / Vraag 12
Quelle est la sécurité cardiovasculaire de l'administration de suppléments calciques ?
Zijn calciumsupplementen veilig voor hart en bloedvaten?

Question 13 / Vraag 13
Comment le pharmacien (d'officine publique) peut-il contribuer à la bonne gestion de l'administration de suppléments de vitamine D et de calcium ?
Hoe kan de apotheker (van een open officina) de toediening van vitamine-D- en calciumsupplementen optimaal begeleiden?

1.1.2 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:
- To discuss selected guidelines regarding jury questions number 1--7, 9-13
- To search for systematic reviews, meta-analyses and RCT's concerning the benefit of vitamin D or calcium supplements on a number of outcomes related to bone health. These topics are fractures (hip, vertebral, non-vertebral fractures) and falls.
- To search for systematic reviews, meta-analyses and RCT's concerning the risks of calcium supplements regarding cardiovascular health.

1.1.2.1 Populations
The following populations are to be evaluated:

- Older populations, with or without osteoporosis, living in community or institutionalised, from industrialised countries.

Excluded from the literature search are:
- Children
- Pregnant women
- Patients with secondary osteoporosis
- Patients from developing countries
- Patient populations of whom 100% are taking medication affecting bone metabolism

1.1.2.2. Interventions
Only products with a registered indication in Belgium will be considered. In Belgium only cholecalciferol (vitamin D3) is a first line product. Other forms of vitamin D are available (like calcitriol) but are only given for certain specific diagnoses.
For calcium, all calcium salts are considered.

Interventions can be:

- Vitamin D3 alone
- Calcium alone
- Associations of vitamin D3 en calcium

Possible comparisons are:

- Vit D3 vs placebo
- Vit D3+ Calcium vs placebo
- Vit D3 + Calcium vs Calcium
- Vit D3 + Calcium vs vit D3
- Calcium vs placebo

1.1.2.3 Endpoints

The following endpoints are to be reported from RCT's:

- Total mortality
- Fractures (hip, vertebral, non-vertebral, all fractures)
- Falls (rate of falls, number of fallers)

For calcium, additional endpoint need to be reported:

- Cardiovascular events (stroke, myocardial infarction)

1.1.2.4 Study criteria

All types of studies

- Research question in selected publication matched research question for this literature review
- Reporting of clinically relevant outcomes
- Some publications were excluded for practical reasons:
  - Publications unavailable in Belgian libraries
  - Publications in languages other than Dutch, French, German and English

RCT

- Preferably double blind, but for strong endpoints like fractures single blind is authorized.
- Minimum follow-up of 1 year
- Minimum number of participants: minimum 40 per study arm. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.
- Phase III trials

Observational studies were not considered.

1.1.2.5 Guidelines

Only guidelines that report Levels of evidence/Grades of recommendation are selected.
Only guidelines from 2009 onwards are selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

Each guideline will be appraised on base of the AGREE II scoring system, with special attention to the evidence supporting the Levels of evidence and the Grades of recommendation.

In order to make an assessment on the rigour of development of the guidelines, guidelines were scored according to Agree II score, for the domain "Rigour of development". More information can be found on http://www.agreetrust.org/[1]
Table 1 gives an overview of the items assessed in this domain according to the Agree II score.

Item	Rigour of development
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table 1: items assessed by the domain "rigour of development" according to Agree II score

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score "Rigour of development" can be used to assess the methods used to develop the recommendations, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable.

In the section about the guidelines, the Domain scores like assessed by the literature group, are given for each guideline.

1.2 Search strategy

1.2.1 Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we searched for large systematic reviews from reliable EBM-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. For the subjects where we didn't find systematic reviews in this manner, Pubmed was searched using the query and limited to systematic reviews. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for RCT's, meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched:

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link "evidence-based guidelines" on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to 'guideline search engines', like National Guideline Clearinghouse and G-I-N.

1.2.2 Details search strategy

The following systematic reviews or meta-analyses were selected as source documents:

<u>Vitamin D3 en fractures</u>

– Avenell, A., Mak, J.C.S. & O'Connell, D., 2014. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *The Cochrane database of systematic reviews*, 4, p.CD000227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24729336.
(search date November 2012)[2]

Vitamin D, Calcium and falls
– Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for Preventing Falls in Older People Living in the Community. 2012. *The Cochrane Database of Systematic Reviews* 9 (January): CD007146. http://www.ncbi.nlm.nih.gov/pubmed/22972103. (search date March 2012)[3]

– Cameron ID, Murray GR, Gillespie LD, Robertson MC, Hill KD, Cumming RG, Kerse N. Interventions for Preventing Falls in Older People in Nursing Care Facilities and Hospitals. 2010. *The Cochrane Database of Systematic Reviews* (1): CD005465. (search date March 2012)[4]

Calcium and fractures
– Tang, B, Eslick G, Nowson C, et al. 2007. "Use of Calcium or Calcium in Combination with Vitamin D Supplementation to Prevent Fractures and Bone Loss in People Aged 50 Years and Older: A Meta-Analysis." *Lancet* 370 (9588) (August 25): 657–66. doi:10.1016/S0140-6736(07)61342-7. http://www.ncbi.nlm.nih.gov/pubmed/17720017. (search date January 2007)[5]

- Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. Am J Clin Nutr 2007;86:1780-90, Dec.[6]

Calcium and mortality / cardiovascular risk
– Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. Effect of Calcium Supplements on Risk of Myocardial Infarction and Cardiovascular Events: Meta-Analysis.2010. *BMJ (Clinical Research Ed.)* (search date march 2010)[7]

– Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. *J Bone Miner Res* 2015;30:165-75, Jan. DOI: 10.1002/jbmr.2311. (search date 24 may 2013)[8]

A search strategy was developed in Pubmed to find relevant RCT's that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
The search strategy that was used can be found in the Appendix.

1.3 Selection procedure

Selection of relevant references was conducted by three researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

In– and exclusion criteria of the different types of studies are found in chapter 1.1.2 with relevant populations, interventions, endpoints and study criteria.

1.4 Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence.
The GRADE-system is outcome-centric. This means that quality of evidence is assessed for each endpoint, across studies.

The GRADE-system[9,10,11] assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency		- 1	Important inconsistency
Directness		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of association (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

Table 2: items assessed by the GRADE system

In this literature review the criteria 'publication bias' has not been assessed. The GRADE system has only been used in this literature review to assess RCT's, so the criteria specifically intended for observational studies (see table above) has not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data

SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

Table 3: grade system adapted by literature group

In assessing the different criteria, we have applied the following rules:

Study design

In this literature review GRADE was applied to all selected RCT's.

Study quality

To assess the methodological quality of RCT's, we considered the following criteria:

- **Randomization**: If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?
- **Allocation concealment:** If the method of allocation was described, was it adequately concealed (central allocation, …) or inadequate (open schedule, unsealed envelopes, etc.)?
- **Blinding**: Who was blinded? Participants/personnel/assessors. If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection with no double dummy)?
- **Missing outcome data:** Follow-up, description of exclusions and drop-outs, ITT
- **Selective outcome reporting**

If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCT's that were included in the meta-analysis/systematic review.

Application in GRADE:

Points were deducted if one of the above criteria was considered to generate a high risk of bias for a specific endpoint.

For example:

- Not blinding participants will not decrease validity of the results when considering the endpoint 'mortality', but will decrease validity when considering a subjective endpoint such as pain, so for the endpoint pain, one point will be deducted.
- A low follow-up when no ITT analysis is done, will increase risk of bias, so one point will be deducted in this case.

Consistency

Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account

- Statistical significance
- Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non-significant result in the same direction as the other studies, these results are considered consistent.
- Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

If we include systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision.
For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.
More information on the GRADE Working Group website: http://www.gradeworkinggroup.org[10]

1.5 Synopsis of study results

The complete report contains per research question
- (Comprehensive) summary of selected guidelines
- Evidence tables (English) of systematic reviews or RCT's on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question
- (Brief) summary of selected guidelines
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

2 Critical reflections of the literature group and reading committee

2.1 Population

The majority of clinical studies is done on older, post-menopausal women, community-dwelling as well as institutionalized. Some studies have mixed male and female populations and only one study focussed on men exclusively. Information about the effect on men is therefore less clear. Since the large majority of patients are women, there is the problem of post-menopausal bone loss which can lead more easily to a fracture when patients fall. (However, it is useful to keep in mind that a fracture does not always result from a fall.) BMD measurement or previous fractures (an estimate of the patients' skeletal health) is not always done or reported.

Inclusion and exclusion criteria vary a lot between studies and hinder comparison. This variance leads to heterogeneous groups, and makes it difficult to form conclusions for actual, practical application.

Age: The population in the studies is typically an older population, but there is a lot of heterogeneity between studies. There is often a lower cut-off limit for inclusion at 50 years or menopause for women, but aside from that the studies cover a variety of ages and ranges of fracture risk. This causes some imprecision, as the clinical profile of someone who is 50 years old will not be the same as that of someone who is 80 years old. Still, results are often pooled across diverse populations.

For older age, the difference between people still living in the community and people living in institutions becomes more important. Some interventions that have no effect on people living in community seem to show an effect on people living in institutionalized settings.

A last remark on age is that bone health at older age is directly depends on bone health and calcium status at a younger age. Perhaps the major benefit of calcium and vitamin D can only been seen in the long term, which is more difficult to study, and more expensive to investigate.

Poly-medication: An older population is generally polymedicated, but the other medications participants are taking is rarely reported, even though some medications have an effect on falls [12]. A typical example of this is benzodiazepine use, and it should be noted that a reduction of benzodiazepine prescription is another possible intervention to prevent falls. Some drugs also have an effect on vitamin D levels, like anticonvulsant therapies, and other drugs could heighten risk of fracture (like PPIs) Those medications are sometimes an exclusion criteria, but not always.

People who take medication with an effect on bone (like hormone replacement therapy, selective oestrogen receptor modulators, etc.) were often excluded from the trials, except in some cases like the Women's Health Initiative studies. The latter is also one of the bigger trials and it is often referred to or included in meta-analyses, which increases imprecision and makes results harder to interpret.

Primary or secondary prevention: Studies do not always make the difference between primary and secondary prevention of osteoporotic fractures. Sometimes a study will clearly be set up to examine the effects of primary or secondary prevention, but this isn't always the case and often populations are mixed. It's thus not always possible to separate the evidence for primary and secondary prevention. vIt might make more sense to classify patients or populations according to

fractures risk instead of primary or secondary prevention, but few studies are set up this way.

On top of that, patients who have had an osteoporotic fracture are generally put on some form of treatment to support bone health, like bisphosphonates,. It has not been asked of this literature review to investigate whether or not calcium and vitamin D are helpful add-ons to these kind of medications. It is nevertheless necessary to mention that in almost all studies on the effect of anti-osteoporosis medication (such as bisphosphonates) both intervention and control group were given calcium and vitamin D[13]. This makes it difficult to investigate the effect of calcium and vitamin D in addition to those drugs. Also, in most studies about calcium and vitamin D, taking medication with an effect on bone metabolism is an exclusion criteria.

Vitamin D status: It is generally not taken into account that vitamin D status varies with fat percentage[14]. BMI's are sometimes given when summarising the population characteristics but this doesn't give information on fat percentage. Also, sometimes vitamin D status is not measured and one doesn't know if the study population is deficient or not. A last remark is that how vitamin D-deficient a population tends to be also depends on latitude and sun exposure.

Subgroups: In the chapter on fractures a lot of results from subgroups are reported. Sometimes the analysis happens post-hoc, sometimes subgroups are defined beforehand, or the study populations is selected from a specific subgroup (as seen for secondary prevention of fractures: only selecting people with a previous fracture). Since the effect from calcium and vitamin D is often borderline significant those subgroup analyses can help define the population that could benefit most from those interventions, but caution needs to be taken when generalizing those results.

2.2 Interventions

Although concentrated on calcium and vitamin D, interventions investigated in the meta-analysies can be quite different.

Vitamin D: Vitamin D exists as cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). Our focus is on cholecalciferol, as this form of the vitamin is largely available as medicine and food supplements in Belgium, and there are no medicines containing sufficient ergocalciferol as mono preparations in first line use. Both forms of vitamin D are used and pooled together in the MA.

Different comparisons are also possible and are found in the literature: calcium versus placebo, calcium + vitamin D versus placebo, calcium + vitamin D versus vitamin D, etc. This leads to a fragmentation of the available evidence.

In Belgium weekly, biweekly or monthly dosing regimens are common. A lot of studies use a daily dosing regimen, especially when vitamin D is combined with calcium. However some studies researched dosing regimens where a large dose was administered once a year or once every four months. When pooled together, those studies showed a heightened risk for falls.

Lately there has been a focus on vitamin D in the literature. There are more recent studies with vitamin D as intervention (with or without calcium) than studies where calcium alone is the intervention being evaluated.

Calcium: Supplementation of calcium in the studies is mainly done with calcium carbonate in

sufficient doses (1000 to 1200 mg per day). However sometimes calcium citrate is used for supplementation. Per weight unit, calcium citrate contains less elementary calcium as compared to calcium carbonate: e.g. 500 mg calcium citrate contains only 120 mg calcium. This amount can hardly be distinguished from the dietary intake.

Many studies report poor compliance to the study medication. This is often imputed to the fact the patients are already taking many pills a day. One also needs to keep in mind that calcium supplements can cause constipation, and generate a bad taste. This can be especially deleterious for a population that is already at risk for malnutrition, like frail elderly.

Dietary calcium: A study will often give the mean intake of dietary calcium per day, but not always. Doses from supplements are generally not adapted to dietary calcium intake.

The literature group wishes to point out that different studies with food-based interventions or fortified food products exist. However, those were excluded from this literature review since the assignment was limited to calcium supplements. We wish to stress that diet too can have an important role, as found in many guidelines.

Galenics of vitamin D: This literature review focuses on oral interventions, and those might not be adapted for people with chronic malabsorption (gastric bypass, chronic pancreatitis etc.). Intramuscular injection might be a preferable intervention for this group. This literature group was however not asked to investigate these interventions by themselves. They are sometimes pooled with the results of oral interventions

2.3 Outcomes

Bone Mineral Density is a frequently reported, but surrogate endpoint to define osteoporosis (and fracture risk. EMA discourages the use of BMD as the sole indicator for osteoporosis or fracture risk. Studies where the only endpoint being measured was BMD were excluded for this reason[15].

Concerning the safety of calcium-supplements, only endpoints related to cardiovascular disease were considered. Studies conflict on whether or not calcium supplementation could heighten cardiovascular risk. There is a lot of discussion for this specific aspect of calcium safety, but we wish to insist that it is critical to pay close attention to the included population group. Again, the populations considered are heterogeneous, and makes it hard to form a firm conclusion when results are considered across several studies. Some groups seem to be more at risk, but more studies, with well-defined populations are needed.

Another aspect of cardiovascular health under debate is the blood-pressure lowering effect of calcium supplements[16, 17].

Concerning general health, a lot of attention lately has been going to the positive effects of vitamin D on multiple health outcomes[18] and also for its possible effect on cancer or even mortality[19]. After debate with the organizing committee it was decided that those subjects could be the topic of an expert's opinion but were not for the literature review.

Calcium supplements are known to heighten the risk for kidney stones and other renal problems. This was not investigated by the literature group, since it wasn't linked to a question from the organising committee, and could be considered a shortcoming of this literature study.

2.4 Study design and quality

Studies generally tend to have relatively low risks of bias. Blinding and allocation concealment are often well presented and executed.

The power of studies is often not enough to detect an effect on fractures. This is especially true when studies are primarily aimed at detecting changes in BMD and additionally report fracture data. Smaller studies especially are underpowered (and tend to be of lower overall quality). A recurrent problem with study power is the following: In the early trials of calcium and vitamin D (late 1980 – early 1990) the results seemed promising. Researchers in subsequent studies based their power calculations on those encouraging results, but the amount of events that they then recorded during their own study was lower than expected and calculated. Thus the study did not have enough power to detect a reduction of falls or fractures due to the intervention.

A significant number of studies are funded by grants from public health organisations.

Most obvious, however, is the diversity in population between studies, which weakens meta-analyses where patient populations are pooled together.

2.5 Guidelines

Guidelines differ in their approach; some give recommendations for daily allowances which includes intake by diet and supplements; other for vitamin d supplementation. Also the population considered by the guidelines differ; some consider a healthy population; other patients with a vitamin D deficiency, while few others consider patients who are diagnosed with osteoporosis. This makes it difficult to compare these recommendations and reference values.

Guidelines often states that there is inadequate evidence to make a recommendation. More studies considering specific populations are needed. For example, specific guidelines for populations over 80 paying special attention to morbidity, self-sufficiency or polypharmacy are lacking.

High age and living situation can also have an impact on upper levels of toxicity. For vitamin D those are often set at 2000 IU per day, but this limit has not been made with patients in mind that have little to no sun exposure, as can be expected from very frail elderly.

Generally the natural annual sinusoidal cycle of vitamin D is not taken into account and recommendations do not vary according to season. It remains unclear whether this could have an effect on bone quality.
The literature group was not petitioned to specifically investigate the two above-mentioned remarks, but literature group and reading committee felt they should be mentioned.

2.6 Other considerations

Vitamin D levels are also influenced by sun exposure, which is difficult to evaluate.

There are differences between techniques used to measure vitamin d and differences between laboratories. This makes it difficult for a clinician to interpret threshold values.

3. General information on selected guidelines

3.1 Selected guidelines

The selected guidelines and their abbreviations like used in this report can be found in table 4.

CBO 2011[20]	CBO richtlijn osteoporose en fractuurpreventie 2011
ICSI 2013[21]	Institute for Clinical Systems Improvement: Diagnosis and treatment of osteoporosis 2013
USPSTF Screening 2014[22]	Screening for Vitamin D Deficiency in Adults: U.S. Preventive Services Task Force Recommendation Statement 2014
USPSTF supplementation 2013[23]	U.S. Preventive Services Task Force Vitamin D and calcium supplementation to prevent fractures in adults 2013
NICE 2013[24]	NICE clinical guideline 161: Assessment and prevention of falls in older people. 2013

Table 4 : abbreviation of selected guidelines

Additionally, reference values from the following guidelines are cited because the above selected guidelines refers to these documents:

IOM 2011[25]	Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D.
HGR NL 2012[26]	Hoge Gezondheidsraad Nederland: Evaluatie van de voedingsnormen voor vitamine D

Table 5 : abbreviation of additional guidelines

The following tables show the development group and target audience for each of the selected guidelines:

CBO 2011	
Development group	Multidisciplinary work group, consisting of representatives of all medical disciplines and advisors of the cbo involved in diagnostics, treatment and support of patients with osteoporosis: General practitioners, endocrinologists, rheumatologists, other medical specialists, pharmacist, patient representative, epidemiologist…
Target audience	All care providers, who are involved in diagnostics, treatment and support of patients with osteoporosis

Table 6: development group and target audience for CBO 2011

ICSI 2013	
Development group	Multidisciplinary work group, consisting of general practitioners, endocrinologists, rheumatologists, pharmacist, internists, nurse, health educator, gynaecologist, facilitator, measurement/implementation advisor.
Target audience	health professionals and other expert audiences.

Table 7: development group and target audience for ICSI 2013

USPSTF supplementation 2013 and USPSTF screening 2014	
Development group	US preventive service task force – independent expert panel
Target audience	Not specified.

Table 8: development group and target audience for USPSTF 2013 and 2014

NICE 2013	
Development group	Multidisciplinary team, members include representatives from nursing, general practice, allied health, NSF working party, falls researchers, falls clinicians, patient groups.
Target audience	Healthcare and other professionals and staff who care for older people who are at risk of falling.

Table 9: development group and target audience for NICE 2013

3.2 AGREE II score

Information about the Agree II score can be found in the section “Methodology”.
A summary of the assessment by the literature group of the individual items for each guideline can be found in table 6.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
CBO 2011[20]	3	3	7	3	7	7	4	7	**41**	**69%**
ICSI 2013[21]	3	1	5	2	7	7	4	7	**36**	**57%**
USPSTF Screening 2014[22]	6	7	7	1	7	7	5	1	**41**	**69%**
USPSTF supplementation 2013[23]	6	7	7	1	7	5	5	1	**39**	**65%**
NICE 2013[24]	6	7	6	5	5	7	5	1	**42**	**71%**

Table 10: Score of the section "Rigour of development" of the Agree score as assessed by the literature group

3.3 Grades of recommendation and levels of evidence

Grades of recommendation and levels of evidence like defined in each guideline, can be found in tables 7- 11.

CBO 2011[20](GRADE)		
Grades of recommendation	Not described.	
Level of evidence	High	Future research unlikely to change confidence in estimate of effect
	Moderate	Further research likely to have an important impact on confidence in estimate of effect and may change the estimate;
	Low	Further research very likely to have a significant impact on the estimate of effect and is likely to change the estimate
	Very Low	The estimate of effect is very uncertain

Table 11: Grades of recommendation and levels of evidence of CBO 2011 guidelines.

CBO 2011 [20](other method)			
Grades of recommendation		Conclusion based on:	
	1	Evidence of level A1 or at least 2 independent studies of level A2 with consistent results	
	2	A study of level A2 or at least two independent studies of level B	
	3	A study of level B or C	
	4	Expert opinion	
Level of evidence		Intervention	Diagnostic
	A1	Systematic review of min. 2 independent studies of level A2	
	A2	Randomized, double blind controlled trial of good quality and sufficient size	Study compared to reference test (golden standard) with predefined cut-off value and independent assessment of the results of the test and the golden standard, considering a sufficient large series of consecutive patients who all had the index and reference test
	B	Controlled study, but still with all the items of A2. (This includes patient control studies and cohortstudies)	Study compared to a reference test, but not all the items of A2
	C	Non –controlled study	
	D	Expert opinion	

Table 12: Grades of recommendation and levels of evidence of CBO 2011 guidelines according to another method than GRADE.
*This classification is only applicable in situations where for ethic or other reasons controlled trials are not possible. If they are possible, the classification for interventions must be applied.

ICSI 2013[21] (GRADE)			
Category	**Quality definitions**	**Strong Recommendation**	**Weak Recommendation**
High Quality of evidence	Future research is very unlikely to change our confidence in the estimate of effect	The work group is confident that the desirable effects of adhering to this recommendation outweigh the undesirable effects. This is a strong recommendation for or against. This applies to most patients	The work group recognizes that the evidence, though of high quality, shows a balance between estimates of harms and benefits. The best action will depend on local circumstances, patient values or preferences.
Moderate Quality of evidence	Further research likely to have an important impact on our confidence in the estimate of effect and may change the estimate;	The work group is confident that the benefits outweigh the risks but recognizes that the evidence has limitations. Further evidence may impact this recommendation	The work group recognizes that there is a balance between estimates of harms and benefits, based on moderate quality of evidence, or that there is uncertainty about the estimates of the harms and benefits of the proposed intervention that may be affected by new evidence. Alternative approaches will likely be better for some patients under some circumstances.
Low Quality of evidence	Further research very likely to have an important impact on our confidence in the estimate of effect and is likely to change. The estimate or any estimate of effect is very uncertain	The work group feels that the evidence consistently indicates the benefit of this action outweighs the harms. This recommendation might change when higher quality evidence becomes available.	The work group recognizes that there is significant uncertainty about the best estimates of benefits and harms.

Table 13: Grades of recommendation and levels of evidence of ICSI 2013 guidelines.

USPSTF supplementation 2013[22] and USPTSF screening 2014[23]			
Grades of recommendation	Grade	Definition	Suggestions for Practice
	A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial	Offer or provide this service
	B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial	Offer or provide this service
	C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
	D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
	I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF recommendation statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.
Levels of certainty	High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.	
	Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors as: - the number, size, or quality of individual studies - inconsistency of findings across individual studies - Limited generalizability of findings to routine primary care practice	

		- Lack of coherence in the chain of evidence As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion
	Low	The available evidence is insufficient to assess the effects on health outcomes, because of: - the limited number or size of studies - Important flaws in study design or methods - inconsistency of findings across individual studies - Gaps in the chain of evidence - Findings not generalizable to routine primary care practice - Lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Table 14: Grades of recommendation and levels of evidence of USPSTF supplementation 2013 and USPTSF screening 2014

NICE 2013[24] (recommendation of vitamin D is amended from 2004)		
Grades of recommendation	Not described.	
Level of evidence	I	Evidence from meta-analysis of randomised controlled trials or at least one randomised controlled trial
	II	Evidence from at least one controlled trial without randomisation or at least one other type of quasi-experimental study
	III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
	IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

Table 15: Grades of recommendation and levels of evidence of NICE 2013

3.4 Included populations – interventions – main outcomes

In tables 12 - 15 the populations, interventions and main outcomes considered in the guidelines are represented.

CBO 2011	
Populations	- Fracture patients - Osteoporosis patients
Interventions	- Fracture prevention: diagnosis underlying osteoporosis, evaluation of fall risk, screening secondary causes of osteoporosis, medication-related advice or no-medication related advice - Use of "FRAX" - Fall risk and prevention - Vitamin D - Medication against osteoporosis
Outcomes	- Fracture - Risk of falls - Adverse events - Quality of life

Table 16: Included population, intervention and main outcomes of CBO 2011 guideline

ICSI 2013	
Populations	- Adults at risk for osteoporosis or with suspected or confirmed osteoporosis
Interventions	- **Diagnosis/Risk Assessment/Evaluation/Screening** o Assessment for and discussion of risk factors for osteoporosis and low-impact fracture o Use of fracture risk assessment tool (FRAX® analysis) o Serial height measurements with a stadiometer o Assessment of posture for kyphosis o Lateral vertebral assessment with dual energy x-ray absorptiometry (DXA) or radiographs of the thoracic and lumbar spine as indicated o Measurement of bone mineral density (BMD) as indicated o Vertebral fracture assessment (VFA) o Laboratory evaluation of patients with osteoporosis to assess for secondary causes of osteoporosis - **Prevention/Treatment** o Shared decision-making o Lifestyle counselling regarding measures to prevent fractures (exercise, smoking cessation, alcohol restriction, dietary counselling, weight, environmental modification to prevent falls, measures to reduce the impact of falls) o Vitamin D and calcium supplementation o Pharmacologic agents: Gonadal hormones, Bisphosphonates, Selective oestrogen receptor modulator (SERM), Calcitonin,

	Parathyroid hormone 1-34, Denosumab o Follow-up BMD testing (with DXA)
Outcomes	- Fracture risk (absolute risk, relative risk, and incidence) - Predictive value of bone mineral density measurements - Bone density, bone loss, bone health, and fracture risk - Adverse effects

Table 17 : Included population, intervention and main outcomes of ICSI 2013 guideline.

USPSTF 2013	
Populations	- Non-institutionalized or community-dwelling asymptomatic adults without a history of fractures. - This recommendation does not apply to the treatment of persons with osteoporosis or vitamin D deficiency.
Interventions	- vitamin D supplementation with or without calcium - The USPSTF did not consider questions relating to adequate daily intake of calcium and vitamin D, nor did it examine the effect of calcium supplementation alone.
Outcomes	- bone health outcomes - adverse effects - no other health outcomes were evaluated

Table 18 : Included population, intervention and main outcomes of USPSTF 2013.

USPSTPF screening 2014	
Populations	- community-dwelling, non-pregnant adults aged 18 years or older who are seen in primary care settings and are not known to have signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended.
Interventions	- screening for and treatment of vitamin D deficiency, including the benefits and harms of screening and early treatment.
Outcomes	- benefits and harms

Table 19: Included population, intervention and main outcomes of USPSTF 2014.

NICE 2013	
Populations	- All people aged 65 or older are covered by all guideline recommendations. This is because people aged 65 and older have the highest risk of falling. - People aged 50 to 64 who are admitted to hospital and are judged by a clinician to be at higher risk of falling because of an underlying condition are also covered by the guideline recommendations about assessing and preventing falls in older people during a hospital stay.
Interventions	- exercise, including balance training - multifactorial interventions – packages of care, for example, exercise, - education and home modifications - vision assessment and correction of impaired vision - home hazard assessment and modification

	- patient and staff education - medication review - hip protectors - rehabilitation strategies.
Outcomes	- Rate of falls (and proportion of people who fall) - Impact of falls and complications as a consequence of falls - Mortality - Patient satisfaction and experience of falls, prevention, interventions and strategies - Quality of life (for example, fear, confidence and functioning) - Activities of daily living - Adherence to falls, prevention strategies (by patients, healthcare professionals and other staff) - Resource use and cost (for example, length of stay)

Table 20: Included population, intervention and main outcome of NICE 2013 guideline.

3.5 Method of reporting of recommendations and notes

Formal recommendations are written **boldfaced**. Some discussion or extra information from the plain text or tables is summarized in *italics*, to make a difference with the recommendations. These parts must in no case be considered as recommendations because there are neither Grades of recommendation nor Levels of evidence given. The literature group also tried to explain on which evidence the recommendations are founded. If the guidelines refer to studies that are also selected by the literature group, no detailed description will be given in the section of the guidelines, but the reader is directed to the evidence tables of the study.

Guidelines include different populations, from healthy individuals without any risk factors, to individuals at risk for vitamin D deficiency or at risk of osteoporosis, and to individuals with known osteoporosis. An overview of the populations is found in the section 'General information on the guidelines'. Attention to this differences of considered populations is needed for the correct interpretation of the recommendations. Further differences between guidelines are the consideration of daily dietary needs for vitamin D; or the consideration of the dose of vitamin D in case of supplementation. Moreover, some guidelines consider prevention of vitamin D deficiency; other prevention of osteoporosis…

The literature group tried to make a concluding summary for each section, but the above mentioned differences make it difficult to compare the guidelines and in the summary, important details can be lost and it is advisable to focus on the entire text.

4. Results: Guidelines

In this chapter we present the recommendations as extracted and analysed from different guidelines.

4.1 Screening, measurements, follow up

4.1.1 CBO 2011

In patients with osteoporosis, frequently (30-60%) there are secondary causes. Sometimes they are already known, but in many cases further investigation shows new underlying causes. (Level 2)[20]

In patients of 50 years or older with a fracture and an indication for treatment based on a T-score and/or a vertebral fracture, it is advisable to search for and treat secondary causes of osteoporosis, before starting pharmacological therapy to prevent fractures. Among other laboratory investigations, CBO advises to measure serum calcium and 25(OH) D before start of the medication. In case of laboratory abnormalities, CBO advises to treat the underlying disorder or if necessary to refer the patient to a specialist.[20]

CBO refers to studies which showed that vitamin D insufficiency was an important cause of secondary osteoporosis in patients with fractures.[20]
CBO chooses not to measure and follow up the levels of vitamin D during therapy, because of the costs, the lack of international consensus about the threshold value of an adequate vitamin D level, the differences between a measurement in the summer and the winter, and the variability of the measurements.[20]

4.1.2. ICSI 2013

An initial screening laboratory profile should be considered in all patients with osteoporosis. *(Strong Recommendation, Low Quality Evidence)*[21]

ICSI recommends an initial laboratory evaluation for all patients with osteoporosis without prior workup:

- *25 (OH) D levels: Optimal level is greater than or equal to 30 ng/ml (75 nmol/l) in most patients.*
  - *Serum calcium: To rule out hypocalcaemia (in malabsorption/vitamin D deficiency) or hypercalcaemia (in hyperparathyroidism).*
  - *24-hour urine calcium excretion:*
    - *Low in a malabsorption state (such as in celiac disease or after gastric bypass), in vitamin D deficiency or in patients on thiazide diuretics.*
    - *High in idiopathic hypercalciuria (which is a correctable cause of bone loss) in primary hyperparathyroidism and commonly in patients with excessive calcium intake.*

***Routine monitoring of vitamin D levels after reaching target levels is not necessary. [Moderate Quality Evidence]*[21]**

4.1.3 USPSTF Screening 2014[22]

The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. (I statement)

This recommendation applies to community dwelling, non-pregnant adults aged 18 years or older who are seen in primary care settings and are not known to have signs or symptoms of vitamin D deficiency or conditions for which vitamin D treatment is recommended.

Risk assessment

Although there is not enough evidence to support screening for vitamin D deficiency, the USTSPF declares that some evidence suggests factors that may increase risk for vitamin D deficiency. Persons with low vitamin D intake, decreased vitamin D absorption, and little or no sun exposure may be at increased risk for vitamin D deficiency. Obesity and darker skin pigmentation may be associated with low levels of serum 25-[OH]D, but it is not clear whether low levels in these populations reflect vitamin D deficiency or are associated with adverse clinical outcomes.

Balance of benefits and harms

The USPSTF found no studies that evaluated the direct benefit of screening for vitamin D deficiency in adults. The USPSTF found adequate evidence that treatment of asymptomatic vitamin D deficiency has no benefit on cancer, type 2 diabetes mellitus, risk for death in community-dwelling adults, and risk for fractures in persons not selected on the basis of being at high risk for fractures. The USPSTF found inadequate evidence on the benefit of treatment of asymptomatic vitamin D deficiency on other outcomes, including psychosocial and physical functioning.

The USPSTF found no studies that evaluated the direct harms of screening for vitamin D deficiency. The USPSTF found adequate evidence that the harms of treatment of vitamin D deficiency are small to none; no studies reporting on the harms of treatment of vitamin D deficiency identified a significant increase in total adverse events, hypercalcaemia, kidney stones, or gastrointestinal symptoms. Screening may misclassify persons and result in over- or underdiagnoses.[22]

4.1.4 Summary

Guidelines recommend to measure calcium and vitamin D in osteoporosis patients before the start of treatment. Follow-up of vitamin D during therapy or after reaching target levels is not necessary. (CBO 2011[20], ICSI 2013[21])

The current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults. (USPSTF screening 2014[22])

4.2 Definition of vitamin D deficiency, threshold and target values of vitamin D, laboratory methods

4.2.1 CBO 2011[20]

For target levels, the CBO refers to the Health Council of the Netherlands[2]. This institution defined target levels for vitamin D as minimum 30 nmol/l (12 ng/ml) for adults and minimum 50 nmol/l (20 ng/ml) for women older than 50 years and men older than 70 years. If the levels are measured (despite the argumentation in section 4.1.1), CBO advises to supplement in such a way that the 25(OH) D level is above 50 nmol/l during the entire year.[20]

4.2.2 ICSI 2013[21]

Target levels for optimum 25-OH vitamin D are according to ICSI 30 ng/mL and often require oral supplementation of 800-1,000 international units. This recommendation is based on the level of vitamin D at which secondary hyperparathyroidism no longer occurs in most people. [Moderate Quality Evidence][21]

4.2.3 USPSTF screening 2014[22]

According to the USPSTF, no consensus exists on the definition of vitamin D deficiency or the optimal level of total serum 25-(OH)D. The USPSTF does not endorse the use of a specific threshold to identify it.[22] The USPSTF refers to the Institute of Medicine[8], who concluded that total serum 25-(OH)D levels of 40 nmol/L (16 ng/mL) meet the needs of approximately half of the population, and levels of 50 nmol/L (20 ng/ mL) or greater meet the needs of nearly all of the population.[27]

The USPSTF indicates that vitamin D level results vary by testing method and between laboratories using the same testing methods. It is unclear if total serum 25-(OH) D is the best indicator of vitamin D status or if bioavailable 25-(OH) D should be used instead.[22]

4.2.4 Summary

No firm recommendations are given for the threshold and target levels of vitamin D.
In text, the guidelines mention as optimum vitamin D level

- In adults, min. 30 nmol/l (12ng/ml) (HGR NL 2012)[25]
- In women > 50 years and men > 70 years, min. 50 nmol/l (20ng/ml) (HGR NL 2012)[25]
- ICSI uses higher target levels: 30ng/ml (ICSI 2013)[20]

USPSTF does not endorse the use of a specific threshold for vitamin D deficiency, but indicates that a level of 50 nmol/l (20ng/ml) meet the needs of nearly all of the population. (USPSTF screening 2014[21])

4.3 Vitamin D / calcium and osteoporosis / fractures

4.3.1 Institute of Medicine 2011[27]

The dietary reference intake of the Institute of Medicine was originally not selected by the literature group to be discussed, because no Levels of evidence nor Grades of recommendation are reported. Because other selected guidelines (USPSTF, ICSI) refer to the dietary reference intakes from Institute of Medicine, we represent in table 16 the main results, to which we will refer in the selected guidelines. Reference intake standards for pregnant and breastfeeding women were out of the scoop of this literature search.

Institute of Medicine recommended daily dose 2011		**Vitamin D (IU)**
Women	19-50 y	600
	51-70y	600
	>70y	800
Men	19-50 y	600
	51-70y	600
	>70y	800

Table 21: Recommended daily dose of vitamin and calcium by the Institute of Medicine

Assuming minimal sun exposure, daily dietary vitamin D intake of 600 IU in adults aged 18 to 70 years and 800 IU in adults older than 70 years should be sufficient to meet the needs of 97.5% of the adult population.[22]

4.3.2 CBO 2011[20]

4.3.2.1 Calcium

Calcium supplementation reduces the chance of non-vertebral fractures, but the effect is larger in combination with vitamin D (HIGH quality of evidence)[1]

Calcium reduces only in combination with vitamin D the occurrence of hip fractures. (HIGH quality of evidence) [20]

It is advisable that patients with osteoporosis use a calcium supplement of 500 or 1000 mg per day if the dietary intake of calcium is lower than 1000-1200 mg per day. The supplementation dose of 1000 mg applies especially if the patient uses no dairy products at all.

The literature group indicates that this recommendation concerns patients with osteoporosis.

CBO evaluated the effect of calcium supplementation on the base of 3 meta-analyses. The meta-analysis by Tang et al 2007[5] and the one by Bischoff-Ferrari 2007[6] are discussed in the evidence tables in chapter 5. CBO also mentions a meta-analysis of Boonen at al[28], which showed that vitamin D alone does not change the risk of hip fractures, but the addition of calcium to vitamin D leads to a reduction of hip fractures.[20]

The CBO considers 4 dairy products per day sufficient, (1000-1200mg calcium), otherwise calcium supplementation is necessary; in practice 500 mg per day is usually sufficient. Sometimes referral to a dietician can be considered, for a dietary advice.

4.3.2.2 Vitamin D

Supplementation of 400-800 IU vitamin D per day in the elderly (>65 years), in combination with calcium, gives a relative reduction in the occurrence of non-vertebral fractures of 10-20 %.(HIGH quality of evidence)[20]

For the daily supplementation of vitamin D, CBO refers to the report of the Health Council of the Netherlands of 2008. In 2012, the Health Council published a new advice[2]. Consequently, the literature group has chosen not to report the references given by CBO, but to communicate the daily supplementation that is given by the new report of the Health council, in table 17. Be aware that these supplementations concern healthy individuals. [26]The intake of vitamin D needs to stay below the safe upper limit of intake. (2000 IE = 50 µg/d).

For elderly aged >70 years, HGR NL states that there are convincing evidence for the supplementation of vitamin D. For women 50-70 years, no firm evidence exists, but the HGR NL advices supplements just to be on the safe side.[2]

Tabel Dagelijkse behoefte voor vitamine D en bijbehorende aanbevelingen voor suppletie (microgram per dag).

Groep	Criterium	Dagelijkse behoefte [a]	Niveau van suppletie	
			Lichte huid met voldoende zonlichtbloot-stelling [b]	Lichte huid met onvoldoende zonlichtbloot-stelling of donkere huid
0 tot 4 jaar	Risico rachitis en serum 25OHD-gehalte > 30 nmol/l	10	10	10
4 tot 50 jaar (vrouwen) en tot 70 jaar (mannen)	Serum 25OHD-gehalte > 30 nmol/l en totale voorziening	10 [c]	0	10
50-70 jaar vrouwen	Serum 25OHD-gehalte > 30 nmol/l en totale voorziening	10	10 [d]	10 [d]
Vanaf 70 jaar	Risico op botbreuken en serum 25OHD-gehalte > 50 nmol/l	20 [e]	20 [d]	20
Zwangere vrouwen	Serum 25OHD-gehalte > 30 nmol/l	10	10	10

a Onvoldoende zonlichtblootstelling is gedefinieerd als dagelijks minder dan 15 tot 30 minuten blootstelling aan hoog staande zon (tussen 11.00 en 15.00 uur) met hoofd en handen ontbloot bij alledaagse activiteiten. Voor kinderen en volwassenen van 4-50 jaar (vrouwen) en 70 jaar (mannen) geldt dat zij bij voldoende buitenkomen ongeveer twee derde van hun behoefte uit blootstelling van de huid aan zonlicht verkrijgen en ongeveer een derde via de voeding, gemiddeld over het hele jaar.

b Bij het blootstellen aan zonlicht is het van groot belang de aanbevelingen van de KWF Kankerbestrijding op te volgen, waarin wordt afgeraden om kinderen onbeschermd aan een hoog staande zon bloot te stellen, vanwege de kwetsbare kinderhuid en het risico op huidkanker.

c In vergelijking met de voedingsnormen uit 2000 is dit een verhoging van 5 naar 10 microgram vitamine D per dag voor personen van 4 tot 50 jaar. Dit heeft te maken met nieuwe gegevens die sinds 2000 beschikbaar zijn gekomen over de relatie tussen de vitamine D-inname en het serum 25OHD-gehalte en de bijdrage van zonlicht aan de vitamine D-voorziening.

d Dit advies is ten opzichte van het vorige uit 2008 vereenvoudigd met het oog op communicatie.

e In vergelijking met de voedingsnormen uit 2000 is dit een verhoging van 15 naar 20 microgram vitamine D per dag. Dit heeft te maken met nieuwe gegevens die sinds 2000 beschikbaar zijn gekomen over de relatie tussen de vitamine D-inname en het serum 25OHD-gehalte.

Table 22: Recommended daily supplementation of vitamin D according to the Health Council of the Netherlands

It is unclear whether the reduction in non-vertebral fractures is larger for elderly in care facilities than in elderly living in the community. (MODERATE quality of evidence) It is advisable that people living in care facilities use a vitamin D supplement of 800 IU per day.[20]

Although there is no convincing evidence for a higher effectivity of vitamin D supplements in residents in nursing homes, CBO considers vitamin D supplementation with 800 IU advisable, because it is plausible that these patients have a lower vitamin D level.[20]

It is advisable that patients with osteoporosis use a vitamin D supplement of 800 IU per day. [20]

An exception is made for patients where laboratory tests show that the 25 (OH) D levels are high enough. (During the winter > 50 nmol/l). [20]

CBO states that there is sufficient evidence to postulate that supplementation of 800 IU

vitamin D per day is better than 400 IU, considering prevention of fractures. [20]

CBO refers to several meta-analyses (Bischoff-Ferrari 2007[6] and Tang2007[5] (see evidence tables in chapter 5) , Avenell 2009[29] (updated version 2014[2] see evidence tables chapter 5), Abrahamsen 2010[30].

In case of a treatment with osteoporosis medication, sufficient intake of calcium and vitamin D is necessary.[20]

CBO states that sometimes a higher dose of vitamin D can be important in patients with very low vitamin D levels (25(OH)D < 15 nmol/l), who start with a bisphosphonate. For example 10 000 IU/d during 10 days can be considered. Based on several RCT's, the CBO adds that the effectivity of high doses once a year of a half-year is not demonstrated. Higher doses could even harm like a higher fracture or fall risk.[20]

In all studies with bisphosphonates, both intervention and placebo groups were prescribed vitamin D and calcium, on top of the bisphosphonate (or placebo). CBO also remarks that the effect of vitamin D and calcium on the incidence of fractures is limited, but occurs almost without side effects and no toxic effects are perceived at the recommended doses. [20]

4.3.3 ICSI 2013[21]

Adequate calcium and vitamin D intake as well as regular exercise should be discussed with patients for the prevention of osteoporosis (Strong Recommendation, Moderate Quality Evidence).[21]

This recommendation considers primary prevention of osteoporosis.

For recommendations of adequate daily dose of vitamin D, ICSI uses the recommendations of the Institute of Medicine 2011[27] in table 16. ICSI refers to a meta-analysis by Bischoff-Ferrari 2005[31] to found this recommendation.

For the literature group, it is not clear from the guideline if supplementation is always needed if daily doses are not met.[21]

Based on a narrative review, ICSI adds that the high-risk group, i.e. the elderly, long-term care residents and those with no sunlight exposure, would be expected to receive the greatest benefit from vitamin D supplementation.[21]

Diet deficient in vitamin D or calcium without adequate supplementation is according to ICSI a risk factor for osteoporosis and osteoporotic fracture.[21]

Target levels for optimum 25-OH vitamin D stated by ICSI are 30 ng/ml and often require oral supplementation of 800-1,000 international units. However, most multivitamins contain 200 to 400 international units. [Moderate Quality Evidence][21]

ICSI also states that there is some controversy over whether vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) is more effective.[21]

According to ICSI, it is also important to ensure adequate vitamin D stores and to correct hypocalcaemia prior to initiation of advanced pharmacologic osteoporosis therapies.[21]

A balanced diet including dairy products and appropriate nutrition should be discussed with patients (Strong Recommendation, Low Quality Evidence)[21]

This recommendation considers patients with elevated risk of fracture.

ICSI refers to narrative comprehensive reviews, that reported that sufficient amounts of calcium slows age-related bone loss and may reduce osteoporotic fracture risk. Both dairy sources and calcium supplements are related to promoting bone health. Diet deficient in calcium (or vitamin D) without adequate supplementation is according to ICSI a risk factor

for osteoporosis and osteoporotic fractures.
For calcium dietary and supplement recommendations <u>for the general population</u>, ICSI refers to the daily intake of the Institute of Medicine[27] in table 16.
For calcium and Vitamin D dietary and supplement recommendations <u>for those at risk for bone loss</u>, ICSI refers to the recommendations of the National Osteoporosis Foundation:

	Calcium	Vitamin D
Adults under age 50	1,000 mg/day	400 IU/day to 800 IU/day
Adults age 50 and older	1,200 mg/day	800 IU/day to 1,000 IU/day

Table 23: Calcium and vitamin D dietary and supplement recommendations for those at risk for bone loss.

When dietary sources do not provide enough calcium, supplements can be used to meet this goal but the first choice is to achieve adequate calcium with diet alone if possible. A variety of foods containing calcium is recommended. ICSI also points to the differences in bioavailability of calcium in food sources and supplements, which is affected by meals, dose size and tablet disintegration. Calcium absorption efficiency decreases at doses greater than 600 mg; therefore, supplements should be taken with meals and in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones and may not be well absorbed. Absorption of calcium carbonate may be decreased in the environment of achlorhydria, high-dose proton-pump inhibitor use or histamine receptor blockers when calcium supplement is taken on an empty stomach. Calcium citrate is better absorbed by patients with medication-induced achlorhydria.

4.3.4 USPSTF supplementation 2013[23] and screening 2014[22]

The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or in men. (I statement)[23]
The USPSTF concludes that the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with greater than 400 IU of vitamin D_3 and greater than 1000 mg of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women. (I statement)[23]
The USPSTF recommends against daily supplementation with 400 IU or less of vitamin D_3 and 1000 mg or less of calcium for the primary prevention of fractures in non-institutionalized postmenopausal women. (D recommendation)[23]

The USPSTF recognizes that appropriate intake of vitamin D and calcium are essential to overall health.
Besides oral vitamin D, the USPSTF mentions increasing dietary vitamin D intake or sun exposure as treatment options, although sun exposure is not generally recommended because it can increase the risk for skin cancer.

Recommendations are based on a meta-analysis carried out for the USPSTF which showed no statistically significant reduction in fractures in case of vitamin D and calcium supplementation in primary prevention in community-dwelling adults. In the largest trial, doses were 400 IU of vitamin D_3 and 1000 mg of calcium daily. Due to the lack of effect on fracture incidence and the increased incidence of nephrolithiasis in the intervention group of the WHI trial[32], the USPSTF concludes with moderate certainty that daily supplementation with 400 IU of vitamin D_3 and 1000 mg of calcium has no net benefit for

the primary prevention of fractures in non-institutionalized, postmenopausal women.[23]
Trials of vitamin D supplementation alone showed no statistical difference. Neither baseline vitamin D status nor supplement dose correlated with supplement efficacy.
USPSTF refer to the daily dose of vitamin D recommended by the Institute of Medicine see table 16.

The USPSTF states that research is needed to determine whether daily supplementation with greater than 400 IU of vitamin D3 and greater than 1000 mg of calcium reduces fracture incidence in postmenopausal women or older men. The comparative effectiveness of different preparations of vitamin D or different calcium formulations should be evaluated. Prospective studies should assess the potential benefits of vitamin D and calcium supplementation in early adulthood on fracture incidence later in life. Studies are needed to evaluate the effects of vitamin D supplementation in diverse populations[23]

4.3.5 Summary

4.3.5.1 Calcium

Considering recommended daily dose of calcium

Population	Recommended daily dose of calcium by most guidelines	Alternative
Aged ≤50y	1000mg	
♂50-70 y	1000mg	1200 mg/day if at risk for bone loss (ICSI)
♀>50y, ♂>70 y	1200mg	

Table 24: recommended daily dose of calcium

The role of a balanced diet including dairy products to meet this recommended daily dose is mentioned by the guidelines (ICSI 2013[21], CBO 2011[20]).

Considering primary prevention of fractures

Two approaches can be found in the guidelines.
The first approach by ICSI points to the above recommended daily dose of calcium, and states that in case dietary sources do not provide enough calcium, supplements can be used.[21]
The second by USPSTF focuses the supplementation with calcium and concludes

- in premenopausal women or in men, the current evidence is insufficient
- in non-institutionalized postmenopausal women, the current evidence is insufficient considering doses > 1000 mg of calcium, and supplementation with ≤1000mg Calcium is not recommended[23]

Considering patients with osteoporosis

It is advisable to use a calcium supplement of 500 or 1000 mg per day if the dietary intake of calcium is lower than 1000-1200 mg per day. (CBO 2011[20], ICSI 2013[21]) In case of a treatment with osteoporosis medication, sufficient intake of calcium is necessary. (CBO 2011[20])

4.3.5.2 Vitamin D

Considering recommended daily dose of vitamin D
(total by sun exposure, diet and supplements)

Population	Recommended daily dose of vitamin D (different according to guidelines)
aged ≤50y	400 (HGR NL 2012[25]), 600 (IOM 2011[24], ICSI 2013[21], USPTF supplementation 2013[23]), 800 IU (ICSI 2013[21] if at risk for bone loss)
50-70 y	400 (HGR NL 2012[26]), 600 (IOM 2011[27] ICSI 2013[21], USPTF supplementation 2013[23]), 800 to 1000 IU (ICSI 2013[21]if at risk for bone loss)
>70 y	800 (IOM 2011[27], HGR NL 2012[26] ICSI 2013[21], USPTF supplementation 2013[23]) to 1000 IU (ICSI 2013[21] if at risk for bone loss)

Table 25: recommended daily dose of vitamin D

If above daily dose is not met by sun exposure or dietary sources, it is not clear from all the guidelines if supplementation is necessary in the primary prevention of fractures. The recommendations considering vitamin D supplements differ across guidelines and can be found in table 22.

Recommended supplementation can be found in the table below.

Population	HGR NL 2012[2], CBO 2011[1]	USPSTF supplementation 2013[5]
♀<50y/premenopausal ♂<70 y	400 IU in case of minimal sun exposure	Insufficient evidence
♀ 50-70 y postmenopausal non-institutionalized	400 IU	Insufficient evidence for > 400IU ≤ 400IU is not recommended
>70 y, non-institutionalized	800IU	Insufficient evidence for > 400IU ≤ 400IU is not recommended
Institutionalized	800IU	Population not included
Pts with osteoporosis	800 IU	Population not included

Table 26: recommended supplementation of vitamin D

4.4 Prevention of falls in the elderly

4.4.1 CBO 2011[20]

High doses of vitamin D supplementation (700-1000 IU) are effective in the reduction of the fall risk of elderly, namely if a vitamin D deficiency exists. Low doses (200-600 IU) are not effective. (HIGH Quality of evidence)[20]

The working group believes that fall interventions in people with previous falls have to focus on the factors which are found in a fall risk evaluation. These imply specific actions tailored to the patient. (For example vitamin D supplementation). The working group wants to emphasise that multifactorial fall interventions can prevent falls. It is otherwise not (yet) proven that prevention of falls also prevents fractures.[20]

CBO refers to two meta-analyses. The first, a Cochrane review of Gillespie 2009 has meanwhile been withdrawn and replaced by two other Cochrane reviews which can be found in the evidence tables in section… .The second is a meta-analysis[33] about low and high doses of vitamin D.

4.4.2 ICSI 2013[21]

ICSI states that the role of vitamin D in fall prevention remains unclear. The data available for vitamin D supplementation is inconsistent.[21]

4.4.3 USPSTF Supplementation 2013[23]

The USPSTF recommends vitamin D supplementation to prevent falls in community-dwelling adults aged 65 years or older who are at increased risk for falls because of a history of recent falls or vitamin D deficiency (B recommendation) The median dose of vitamin D in available studies was 800 IU. [23]

4.4.4 Nice 2013[24]

NICE does not recommend implementation of vitamin D supplementation at present in the prevention of falls in older people. This is not because there is strong evidence against it, but because there is insufficient or conflicting evidence supporting supplementation. There is evidence that vitamin D deficiency and insufficiency are common among older people and that, when present, they impair muscle strength and possibly neuromuscular function, via CNS-mediated pathways. In addition, the use of combined calcium and vitamin D_3 supplementation has been found to reduce fracture rates in older people in residential/nursing homes and sheltered accommodation. Although there is emerging evidence that correction of vitamin D deficiency or insufficiency may reduce the propensity for falling, there is uncertainty about the relative contribution to fracture reduction via this mechanism (as opposed to bone mass) and about the dose and route of administration required. No firm recommendation can therefore currently be made on its use for this indication. [2004, amended 2013] (LEVEL I)[24]

4.4.5 Summary

Guidelines differ in their opinion considering vitamin D supplementation in the prevention of falls in the elderly.
Two guidelines state that there is insufficient evidence to recommend it. (NICE 2013[24], ICSI 2014[21]
Two other guidelines state that high doses of vitamin D are effective in the reduction of the fall risk of elderly in case of vitamin D deficiency. (CBO 2011[20], USPSTF supplementation 2013[23])

4.5 Cardiovascular safety of calcium supplements

4.5.1. CBO 2011[20]

CBO states that supplementation of 1000 mg of calcium in postmenopausal women with a mean dietary calcium intake of 850 mg per day may possibly lead to a higher chance of myocardial infarction and CVA. They refer to the meta-analysis of Bolland[7], which can be found in the evidence tables in chapter 7.

4.5.2 ICSI 2013[21]

ICSI declares that calcium supplementation has been shown to increase the ratio of HDL/LDL cholesterol by almost 20% in healthy postmenopausal women by binding to fatty acids in the gut. The effect of calcium supplementation on cardiac risk is unclear at this time. Over-supplementation may be associated with an increased risk of kidney stones and vascular calcification. Besides the meta-analysis of Bolland[7], ICSI also mentions a meta-analysis by Heaney 2012[34] that concluded that a causal inference between calcium and CVD is not currently warranted.[21]

4.5.3 USPSTF supplementation 2013[23]

Just like the guidelines above, USPSTF reports the meta-analysis of Bolland (see evidence tables in chapter 7) which suggests an association between calcium use and increased risk for cardiovascular disease, but the link has not been consistently demonstrated. The effect was primarily seen in persons taking calcium alone and not in combination with vitamin D. None of the studies reviewed by the USPSTF reported this adverse effect.[23]

4.5.4 Summary

Guidelines make no formal recommendation considering calcium supplements and cardiovascular risk. Guidelines refer to the meta-analysis of Bolland[7], which suggests an association between calcium supplementation and cardiac risk, but mention that this association is still unclear.

4.6 Follow-up of vitamin D and Calcium by the pharmacist

No information found in the selected guidelines

5. RESULTS: CALCIUM AND VITAMIN D FOR THE PREVENTION OF FRACTURES

5.1 Calcium versus placebo or no treatment

The evidence for this chapter considering all fractures comes from a meta-analysis by Tang et al, 2007[5]. Evidence concerning hip fractures is provided by the meta-analysis of Bischoff-Ferrari et al, 2007[6]. The latter meta-analysis contains evidence from both cohort studies and RCT's, but we only considered evidence from RCT's. No subgroup analyses were available for primary or secondary prevention alone.
An additional search for new trials published after the search date of the selected meta-analyses was conducted. One extra study was found (Radford, 2014[35]). This study is a follow-up of an RCT mentioned in the meta-analysis by Bischoff-Ferrari (Reid 2006[36]).Full details of the study can be found in section 5.1.3.

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. By Tang B. et al.
August 2007

Search strategy
Searched, without language restrictions through the following databases, until January 2007: Medline, Embase, Current Content, CINAHL (Cumulative index to nursing and allied health care), DARE (Database of Abstracts of reviews of effects), CENTRAL (Cochrane Central Register of Controlled Trials) and the Cochrane Database of Systematic Reviews. Also, hand-searching of the reference lists of every primary study for additional publications, and reviewing abstract booklets and review articles.

Inclusion criteria
- RCT
- Comparison: Calcium or Calcium and vitamin D supplementation
- Versus placebo
- Outcomes: Reported BMD or fractures
- Population: Patients 50 years or older

Calcium intake and hip fracture risk in men and women : a meta-analysis of prospective cohort studies and randomized controlled trials. By Bischoff-Ferrari H., et al.
June 2007

Search strategy (for RCT's)
Systematic search of relevant English and non-English publications using MEDLINE (Ovid and Pubmed) for the period from January 1960 to December 2006 and by using EMBASE for January 1991 to December 2006. The authors also contacted experts in the field and searched reference lists and abstracts presented at the meetings of the American Society for Bone and Mineral Research from 1995 through 2006.

Inclusion criteria's (for RCT's)
- Double blind RCT's
- Any dose of calcium supplementation vs placebo
- Minimum follow-up of 1 year
- > 100 study participants
- Outcomes: non-vertebral fractures, hip fractures

5.1.1 Clinical evidence profile: Calcium vs placebo

Comparison:	**Results**		
Ca vs placebo	**Intervention** Mean (SD) or event rate	**Control** Mean (SD) or event rate	**RR (95% CI)**
Fractures, all (from meta-analysis by Tang et al., 2007)			
Reid 1993[37], Chevalley 1994[38], Recker 1996[39], Riggs 1998[40], Peacock 2000[41], Fujita 2004[42], Record trial group 2005[43], Reid 2006[173], Prince 2006[44]	Total (N = 9, n = 6517)		RR=0.90 (0.80 – 1.00) *NS*
	Fractures = 391 / 2492*	Fractures = 412 / 2556*	
Fractures, non-vertebral (from meta-analysis by Bischoff-Ferrari et al., 2007)			
Chevalley 1994[38], Reid 1995[45], Riggs 1998[40], Record 2005[43], Prince 2006[44], Reid 2006[36]	Total (N = 7, n = 6740)		RR = 0.92 (0.81 – 1.05) *NS*
	Fractures = 388 / 3356	Fractures = 426 / 3384	
Fractures, all (extra studies)			
Radford 2014[173]	Total (N = 1, n = 1408)		RR = 0.86 (0.68 – 1.10) *NS*
	Fractures = 121/698	Fractures = 139/710	
Fractures, hip (from meta-analysis by Bischoff-Ferrari et al., 2007)			
Record Trial group 2005[43], Reid 2006[36], Prince 2006[44], Bischoff-Ferrari 2006[46]	Total (N=5, 6504)		RR= 1.64 (1.02-2.64) *NS*
	Fractures = 83/3237	Fractures = 56/3267	
Fractures, hip (extra studies)			
Radford 2014[35]	Total (N = 1, n = 1408)		RR = 1.09 (0.64 – 1.84) *NS*
	Fractures = 29/698	Fractures = 27/710	

Table 27: clinical evidence table for calcium versus placebo
* Numbers do not add up to 100% of total because of missing data in some variables

5.1.2 Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Bischoff-Ferrari 2006* Design: RCT DB Duration of follow-up: 4 y treatment mean follow up 10.8 years	**<u>Inclusion criteria:</u>** - at least one histologically confirmed large-bowel adenoma removed within preceding 3 months - < 80 years - in good health **<u>Exclusion criteria:</u>** - history of familial polyposis - condition that might be worsened by calcium supplementation	N = 930 **Mean age:** 61±9 **Gender distribution:** women: 258 (29%), men: 669 (71%) **Vitamin D status at baseline:** see exclusion criteria **Bone status (osteoporosis, previous fractures? BMD?)** primary prevention only, patients were switched to bisphosphonates or other after fracture **Calcium intake monitoring?** Assessed: mean intake placebo: 853 mg/d, mean intake intervention: 861 mg/d **Concomitant medication:** no data	*1200mg of calcium carbonate/day (n = 464)* *vs* *placebo (n = 466)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate, computer generated random numbers • **BLINDING:** Adequate • **LOST TO FOLLOW-UP:** 14 (1,5%) • Drop-out and exclusion: 95 (10%) • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral source • **SELECTIVE REPORTING:** no • **Important methodological remarks:** 3 months placebo-run-in, only compliant (>80% of tablets taken) participants deemed eligible. • **Main outcome:** Fracture risk reduction, only significant during treatment phase (HR = 0.28 (95% CI: 0.09 - 0.85)
* Note: the date refers to the publication of the abstract. The full article is published in a 2008 article by Bischoff-Ferrari "Effect of calcium supplementation on fracture risk: a double blind, randomized controlled trial" (*Am J Clin Nutr* 2008;87:1945–51)[46] - but at the time of the meta-analysis (2007) only the abstract was available				

Chevalley 1994[38] Design: RCT DB Duration of follow-up: 18 months	**<u>Inclusion criteria:</u>** - ambulatory - elderly - living in community or retirement homes - previous fracture not resulting from severe trauma (for the previous fracture group) **<u>Exclusion criteria:</u>** - parathyroid, thyroid, hepatic or cardiac disorder, paget's disease of bone -plasma creatinine above 160µmol/l - received treatment with corticosteroids, estrogens, anticonvulsants, calcitonin or fluoride during the year preceding - received vitamin D during the previous 2 months - for patients with hip fracture: fracture resulting from severe trauma - metastases or non- osteoporotic metabolic bone diseases - patients with significant mental impairment	N = 156 **Mean age:** Group without previous fractures: 72,1 +- 0.6 y Group with previous fractures: 78.4 +- 1.0 y **Gender distribution:** 86,2% women **Vitamin D status at baseline:** - no previous fracture group: 59.8 nmol/l +-3.1 - previous fracture group: 52.4 nmol/l +- 2.6 **Bone status :** 63 patients with recent hip fracture (mean 12.3 ± 0.8 days before) **Calcium intake monitoring?** No previous fracture group: 619 mg/day +- 33mg previous fracture group: 594 mg/d +- 39 **Concomitant medication:** no data	*800 mg Ca (as calcium carbonate (n= 63)* *OR* *osseino-mineral complex (n=62)* *vs* *placebo (n=31)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 14% for the non-fractured group, 32% of the group with previous fractures • Described: yes • Balanced: no • **ITT:** no • **FUNDING**: Swiss national science foundation & Robapharm AG (industry funding) • **SELECTIVE REPORTING:** no • **IMPORTANT METHODOLOGICAL REMARKS**: All patients were vitamin D replete because they received a single dose of 300 000 IU before the study
Fujita 2004[42] Design: CT R?	**<u>Inclusion criteria:</u>** - hospitalized elderly women **<u>Exclusion criteria:</u>** - previous compression fracture of the spine L1-L4	N = 58 **Mean age:** 81 **Gender distribution:** 100% female **Vitamin D status at baseline:** no data	*900 mg of Ca as active absorbable algae calcium (n=20)* *vs* *900 mg of Ca as*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Unclear • • **Lost to FOLLOW-UP: not described** • • **ITT:** no • **FUNDING**: undisclosed

Duration of follow-up: 2 years		**Bone status (osteoporosis, previous fractures? BMD?)** diagnosed osteoporosis and fracture **Dietary calcium intake monitoring?** Yes, baseline calcium intake 600 mg/d **Concomitant medication:** no data	*CaCO3 (n=18)* *vs* *placebo (n=20)*	• **SELECTIVE REPORTING:** yes • **Important methodological remarks**: Only reports on spinal fractures. Number of events <10
Peacock 2000[41] Design: RCT DB PL Duration of follow-up: 4 years	**<u>Inclusion criteria:</u>** - independently mobile - over 60 - 60% community-dwelling, 40% institutionalised **<u>Exclusion criteria:</u>** - terminal illness; Paget's disease of bone; recurrent urinary stone disease - having been treated with sodium fluoride, bisphosphonate, steroids,or dilantin; - having had renal disease requiring specific treatment; - being excluded by primary physician	N = 438 **Mean age:** women: 73,7 years men: 75,9 years **Gender distribution:** 72 % women 28 % men **Vitamin D status at baseline:** median serum 25OH vitamin D3: 59 nmol/L radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** both subjects with and without a previous fracture **Calcium intake monitoring?** baseline median calcium intake:546 mg/day **Concomitant medication:** ERT was not a reason for exclusion	*750 mg calcium (n=135)* *vs 600 IU (15 µg 25OH) vitamin D3 (n=132)* *vs* *placebo (n=135)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate, randomized to strata by age, sex, serum 25(OH)D concentration and calcium intake • **BLINDING:** Participants: Adequate • personnel/assessors: Unclear • • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 33% of men, 41% of women • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING:** neutral funding • **SELECTIVE REPORTING:** no, but analysis on pre-specified subgroup (men vs women) • **Other important methodological remarks** • Study's first objective was to detected changes to BMD

Prince 2006[44] Design: RCT DB PL Duration of follow-up: 5 years	**Inclusion criteria:** - women ≥ 70 years - c**ommunity-dwelling** **Exclusion criteria:** - Medical conditions that made it unlikely patients would survive the 5 years of study - participating in another clinical trial - Taking medication that could affect bone mass	N = 1460 **Mean age:** 75 y **Gender distribution:** 100% women **Vitamin D status at baseline:** - measured in a subset using a competitive binding assay using diluted human serum that measures 25-hydroxycholecalciferol and ergocalciferol levels equally - Generally above deficiency level **- Bone status (osteoporosis, previous fractures? BMD?)** Previous fractures (at ≥50y) recorded (approx. 25% of subjects) **Calcium intake monitoring?** Semi-quantitatively assessed by food frequency questionnaire, data shown **Concomitant medication:** no data	*1200 mg/day Ca (n = 730)* *vs* *placebo (n = 730)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate, stratified by whether or not the subject had had a previous fracture • **BLINDING:** Participants :Adequate personnel/assessors: Unclear • **FOLLOW-UP:** • **Lost-to-follow-up, withdrawal and deaths: 16%** • Intervention: 119 subjects, Placebo: 113 subjects • Described: yes • Balanced across groups: yes • **ITT:** no, censored for death and withdrawal + PPA • **FUNDING**: neutral funding • **SELECTIVE REPORTING:** no, but post-hoc analysis of certain subgroups • **Main findings**: In ITT, calcium supplementation did not significantly reduce fracture risk (HR = 0.87; 95% CI: 0.67 - 1.12). • Post-hoc subgroup analysis of compliant subjects (HR= 0.66; 95% CI 0.45 - 0.97)
Recker 1996[39] Design: RCT	**Inclusion criteria:** - Fully ambulatory - Living independently - Older than 60 years - Low Calcium intake <1gram/day **Exclusion criteria:** - Other diagnoses or treatments known to affect the skeleton	N = 197 **Mean age:** 73.5 (+-7.1 y) **Gender distribution:** 100% women **Vitamin D status at baseline:** - only for a randomly chosen subset of 38 members - competitive binding assay	*1200 mg /day Calcium calcium carbonate (n = 91)* *vs* *placebo (n = 100)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • **Lost to follow-up, drop out and exclusions: 9%** • Described: yes • Balanced across groups: U • **ITT:** yes according to author • **FUNDING**: • **SELECTIVE REPORTING:** yes/no

Duration of follow-up: 4.3 years		**Bone status (osteoporosis, previous fractures? BMD?)** clear distinction between subgroups who had a previous fracture and those who don't **Calcium intake monitoring?** <1g/day Ca **Concomitant medication:** unknown		• **Other important methodological remarks** : study measured only spine fracture incidents
The RECORD trial group 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months	**<u>Inclusion criteria:</u>** - osteoporotic fracture in the previous 10 years **Exclusion criteria:** - bed or chair-bound before fracture - cognitive impairment - cancer in the past 10 years with risk of bone metastasis - fracture associated with bone abnormality - hypercalcaemia - renal stone in the past 10 years - life expectancy less than 6 months - individuals known to be leaving the UK - daily intake of more than 200 IU vit D or more than 500 mg of Ca supplements - intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** - measured in a subgroup by straight-phase HPLC - mean: 15.2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*800 IU vit D3* *vs* *(n=1343)* *vs* *800 IU vit D3 & 1000 mg Ca (given as Ca carbonate) (n=1306)* *1000 mg Ca* *vs* *(n= 1311)* *vs* *Placebo* *(n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no

Reid 1993[37] Design: RCT PL Duration of follow-up: 2 years	**Inclusion criteria:** - Post-menopausal women (3 or more years after menopause) - mean dietary calcium intake of 750 mg/day **Exclusion criteria:** - History of disorders of calcium metabolism (including symptomatic vertebral fractures) - Renal, thyroid or hepatic dysfunction - Current systemic disease - HRT in the previous 3 years - Use of supraphysiologic doses of glucocorticoid for >6m - Current use of glucocorticoids, thiazide diuretic or anticonvulsant medication	N = 130 **Mean age**: 58 **Gender distribution**: 100% women **Vitamin D status at baseline**: known, data not, method not given **Bone status** (osteoporosis, previous fractures?) data not reported **Dietary calcium intake monitoring?** Assessed by four day diet diaries, mean dietary intake of 750 mg **Concomitant medication?** No data	*1000 mg / day Calcium (n= 61)* *vs* *Placebo (n= 61)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear, merely states "randomly assigned" • **BLINDING:** Adequate for participants, unclear for assessors • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 6.2% • Described: only the reason for stopping the study • Balanced across groups: unknown • **ITT:** no, only takes into account the 122 women who finished the study • **FUNDING**: Health research council of new zealand, tablets provided by Sandoz • **SELECTIVE REPORTING:** no

Reid 1995[45] Design: RCT PL Duration of follow-up: 4 (2 year extension of Reid 1993)	**<u>Inclusion criteria:</u>** - having participated in the original 2-year study (Reid 1993) - white women - reached menopause more than 3 years earlier **<u>Exclusion criteria:</u>** history of disorders of calcium metabolism - symptomatic vertebral fractures - renal, thyroid or hepatic dysfunction - current systemic disease - use of hormone replacement therapy within the last 3 years - use of supraphysiological doses of glucocorticoid for more than 6 months at any time - current use of any glucocorticoid - current use of anticonvulsant medication - current use of thiazide diuretics	N = 86 **Mean age:** 58 +-4 years **Gender distribution:** 100% women **Vitamin D status at baseline:** 76+-25,8 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** no previous vertebral fracture **Calcium intake monitoring?** 745 ± 298 mg/d **Concomitant medication:** no data	*1000mg/d calcium as calcium gluconate (n=38)* *vs* *placebo (n=40)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate for participants and assessors • **FOLLOW-UP:** • Lost-to follow-up: 10,3% • Described: no • Balanced across groups: unknown • **ITT:** no • **FUNDING**: different neutral funding sources, tablets by Sandoz Pharmaceuticals • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks:** See Reid 1993 for initial screening and study design • Only 11 fracture events

Reid 2006[36] Design: RCT PL DB Duration of follow-up: 5 years	**<u>Inclusion criteria:</u>** - more than 55 years, post-menopausal - not receiving therapy for osteoporosis or taking calcium supplements - free of major ongoing disease - Lumbar spine density not below the age-appropriate normal range **<u>Exclusion criteria:</u>** **- c**reatinine more than 2.3 mg/dL - serum 25-hydroxyvitamin D was lower than 10 µg/L (25 nmol/L)	N = 1471 **Mean age:** 74 years **Gender distribution:** 100% women **Vitamin D status at baseline:** - see exclusion criteria - measured by radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** primary prevention only, (patients were switched to bisphosphonates or other after fracture) **Calcium intake monitoring?** Yes - mean intake placebo: 853 mg/d - mean intake intervention: 861 mg/d **Concomitant medication:** unknown	*1 g of Ca/day as Calcium citrate (n=732)* *vs* *placebo (n=739)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate, participants and assessors • **LOST TO FOLLOW-UP: 10%** • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: undisclosed • **SELECTIVE REPORTING:** no • **Other important methodological remarks**: power calculation would be adequate to detect a 40% decrease in fracture rate • Low compliance over the entire study (58% in placebo group, 55% in verum group)

Riggs 1998[40] Design: RCT Duration of follow-up: 4 years	**Inclusion criteria:** - fully ambulatory - between 61 and 70 years of age - post-menopausal for 10 years or more **Exclusion criteria:** - history of renal lithiasis, impaired renal function, hypercalcemia, or hypercalciuria (>300 mg/24 h) - any disease known to affect bone or calcium metabolism - receiving estrogen, large doses of vitamin D or calcium, or other drugs known to affect bone - a history of use of fluoride or bisphosphonate drugs	N = 236 **Mean age:** 66 years **Gender distribution:** 100% women **Vitamin D status at baseline:** measured by the methods of Eisman et al. and Kumar et al. Mean for intervention 30.4 ±10.5 nm/ml, mean for placebo: 29.7 ± 10.3 nm/ml **Bone status (osteoporosis, previous fractures? BMD?)** No subject had a history of osteoporotic fractures and all had normal BMD values **Dietary calcium intake monitoring?** Assessed by food questionnaire, mean intervention group: 711± 276 mg / day, mean control group 717 ± 295 mg/day supplemental intake up to 500mg/day calcium acceptable **Concomitant medication:** women taking supplementary calcium at ≤500 mg/day and/or vitamin D at ≤800 IU/day at baseline were eligible for inclusion	*1600 mg/day Calcium (as calcium citrate) (n= 119)* *vs* *Placebo (n= 117)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and exclusions: 25 % • Described: yes • Balanced across groups: yes • **ITT:** no, PPA • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** : no power calculation shown

Table 28: characteristics of studies included in evidence profile from meta-analysis

5.1.3 Characteristics of extra studies in the evidence profile, not reported in a meta-analysis

<table>
<tr><th>Study details</th><th>Inclusion / exclusion criteria</th><th>Patients characteristics</th><th>Comparison</th><th>Outcomes</th><th>Study quality</th></tr>
<tr>
<td>Radford 2014[35]

Design: Follow-up of RCT

Duration of follow-up:

Original study: 5 years + additional 5 years of follow up</td>
<td><u>Inclusion criteria</u>:
- Having participated in the study by Reid et al. In 2006
- Over 55 years of age
- >5 years post-menopause
- normal lumbar spine BMD for their age

(see also inclusion criteria in section 5.1.2, Reid 2006)

<u>Exclusion criteria:</u>
- receiving treatment for osteoporosis
- taking calcium supplements
- having another major ongoing disease
- Serum 25(OH)D < 25 nmol/l

(see also exclusion criteria in section 5.1.2, Reid 2006)</td>
<td>N = 1471

Mean age: 74.1 years

Gender distribution:
100% women

Vitamin D status at baseline:
serum 25(OH)D: 22 µg/L

Bone status:
Previous fractures and bone mineral density recorded

Dietary calcium intake?
859 mg / day

Concomitant medication?
Post-trial medication use:
- 41% used calcium supplements (51% of them from originally assigned calcium group)
- 33% used bisphosphonates (50% of them from original calcium-assigned group)</td>
<td>Follow up study, no extra intervention

Primary study: 1000 mg / day calcium citrate

vs placebo</td>
<td>
<table>
<tr><td colspan="2">TOTAL FRACTURES (any site)</td></tr>
<tr><td>Entire follow-up (Reid 2006 + Radford 2014)</td><td>Post-trial period</td></tr>
<tr><td>Calcium: 225/732
Placebo: 246/739</td><td>Calcium: 121/698
Placebo: 139/710</td></tr>
<tr><td>RR = 0.90 (0.75 - 1.07)</td><td>RR = 0.86 (0.68 - 1.10)</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">HIP FRACTURES</td></tr>
<tr><td>Entire follow-up (Reid 2006 + Radford 2014)</td><td>Post-trial period</td></tr>
<tr><td>Calcium: 44/732
Placebo: 32/739</td><td>Calcium: 29/698
Placebo: 27/710</td></tr>
<tr><td>RR = 1.40 (0.89 - 2.21)</td><td>RR = 1.09 (0.64 - 1.84)</td></tr>
</table>
</td>
<td>
• ALLOCATION CONCEALMENT: NA
• RANDOMISATION: NA
• BLINDING: NA

• FOLLOW-UP:
• Lost-to follow-up: 20 %
• Described: yes
• Balanced across groups: yes
• ITT: yes
• FUNDING: neutral funding
• SELECTIVE REPORTING: no
• Other important methodological remarks
</td>
</tr>
</table>

Table 29: characteristics of included studies not from meta-analysis

5.1.4 Summary and conclusions. Calcium versus placebo

Note: results given in i*talic* in these tables come from additional studies, other from the meta-analyses

Calcium versus Placebo			
Bibliography: meta-analysis TANG 2007[5], BISCHOFF-FERRARI 2006[46], Radford 2014[35]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fractures, all *Mixed primary and secondary prevention* (From Tang et al + Radford 2014)	6517 + *1408* (9+*1*)	RR=0.90 (0.80 – 1.00) NS *(RR = 0.86 (0.68 – 1.10)) NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1, diverse patient population Imprecision: OK
Fractures, non-vertebral *Mixed primary and secondary prevention* (From Bischoff-Ferrari 2007)	6740 (7)	RR = 0.92 (0.81 – 1.05) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1, diverse patient population Imprecision: OK
Fractures, hip *Mixed primary and secondary prevention* (From Bischoff-Ferrari et al 2007 + Radford 2014)	6504 + *1408* (5 + *1*)	RR= 1.64 (1.02-2.64) *NS* *(RR = 1.09 (0.64 – 1.84)) NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1, Reid 2006's RR and CI are substantially higher Directness: -1, diverse patient population Imprecision: OK

Table 30: summary table calcium versus placebo

5.2 Vitamin D versus placebo or no treatment

The evidence tables for this chapter come from a meta-analysis by the Cochrane group (Avenell 2014) regarding the efficiency of vitamin D interventions for preventing fractures. Multiple comparisons are evaluated in this Cochrane review, such as vitamin D versus placebo, vitamin D plus calcium versus placebo etc.
In this chapter we present the results for interventions with vitamin D alone, compared with placebo, as well as sub-group analyses for secondary prevention (= participants selected on the basis of a previous fracture).
A search was conducted for new RCTs, starting after the search date of the meta-analysis. No additional studies were identified.

Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. June 2014, By Avenell A. et al.,

Search strategy
The authors searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register (to December 2012), the Cochrane Central Register of Controlled Trials (2012 Issue 12), MEDLINE (1966 to November Week 3 2012), EMBASE (1980 to 2012 Week 50), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to December 2012) and BIOSIS (1985 to 3 January 2013).
In MEDLINE (OVID Web), they combined subject specific terms with the sensitivity-maximising version of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011*), and modified for use in other databases. For this update, the search results were limited to 2007 onwards. Details of the previous search strategies can be found in past versions of the review, most recently Avenell 2009*.
They identified ongoing studies by searching all registers in Current Controlled Trials (December 2012).
They also checked reference lists of articles and contacted active researchers in the field. We handsearched abstracts published in the Journal of Bone and Mineral Research (1986 to 2012 volume 27), Bone (1998 to December 2012), Calcified Tissue International (1998 to December 2012) and Osteoporosis International (1998 to December 2012).
We placed no restrictions on the language of publication

Inclusion criteria
- Randomised or quasi-randomised trials
- Population: post-menopausal women or older men (median age over 65) or both. Trials focused on participants on corticosteroid therapy were excluded.
- Intervention: administration of vitamin D or vitamin D related compound, with or without the administration of calcium supplements
- Outcomes: Hip fracture (primary), any non-vertebral fractures, vertebral fracture or any new fracture (secondary outcomes).

5.2.1 Clinical evidence profile : Vitamin D alone vs placebo or no treatment

Reference: **Avenell 2014[2]**		**Results**		
Comparison: **Vitamin D vs placebo or no treatment**		**Intervention : vitamin D** Mean (SD) or event rate	**Control** Mean (SD) or event rate	**RR (95% CI)**
Fractures, **hip,** *mixed primary and secondaru prevention*				
Avenell 2004[47], Glendenning 2012[48], Harwood 2004*[49], Law 2006*[50], Lips 1996[51], Lyons 2007*[52], Meyer 2002[53], Mitri 2011[54], Peacock 2000[41], RECORD 2005[43], Smith 2007*[55], Trivedi 2003[56], Vital D (Sanders) 2010[57], Witham 2010*[58], Witham 2013[59]		Total (N = 15, n = 27,693)		RR= 1.12 [0.98 – 1.29] *NS*
		Fractures = 405 / 13,809	Fractures = 362 / 13,884	
Fractures, hip, *secondary prevention*				
Avenell 2004[47], Harwood 2004*[49] , Record 2005		Total (N= 3, n= 2820)		RR= 1.08 [0.72 - 1.62] *NS*
		Fractures = 47/1416	Fractures = 43/1404	
Fractures, all, *mixed primary or secondary prevention*				
Avenell 2004[47], Glendenning 2012[48], Harwood 2004*[49], Law 2006*[50], Lips 1996[51], Lyons 2007*[52], Meyer 2002[53], Mitri 2011[54], Peacock 2000[41], RECORD 2005[43], Smith 2007*[55], Trivedi 2003[56], Vital D (Sanders) 2010[174], Witham 2010*[58], Witham 2013[59]		Total (N = 15, n = 28,271)		RR = 1.03 [0.96 – 1.11] *NS*
		Fractures = 1254 / 14,097	Fractures= 1217 / 14,174	
Fractures, all - secondary prevention				
Avenell 2004[47], Harwood 2004*[49], Record 2005[43]		Total (N = 3, n= 2820)		RR = 1.01 [0.84 – 1.21] *NS*
		Fractures = 191 / 1416	Fractures = 188 / 1404	

Table 31: vitamin D versus placebo or no treatment evidence profile

Secondary prevention = trial participants selected on the basis of having had a previous fracture

* = interventions with vitamin D2 as opposed to vitamin D3 in other studies

5.2.2 Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Avenell 2004[173] Design: part RCT part open design PL (partially, study evaluates differences between open label and placebo controlled) Duration of follow-up: 46 months	**Inclusion criteria:** osteoporotic fracture within the last 10 years aged 70 years or older **Exclusion criteria:** - Disease exclusion: bed- or chair-bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of < 7, suffered from cancer likely to metastasise to bone within the previous 10 years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy < 6 months, known to be leaving the UK - Drug exclusions: taking more than 200 IU (5 µg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, HRT, selective oestrogen receptor modulators, or any vitamin D metabolite (such as calcitriol) in the last 5 years; vitamin D by injection in the last year	N = 134 (open design) **Mean age:** 78 years **Gender distribution**: 111 women = 111 (82.8%) , men = 23 (17.2%) **Vitamin D status at baseline:** unknown **Bone status:** previous osteoporotic fracture in the last 10 years **Dietary calcium intake?** No data **Concomitant medication?** No data	*1) Calcium 1000 mg and vitamin D3 800 IU given as 2 tablets(calcium as calcium carbonate) (n=35)* *2) Calcium 1000 mg given as 2 tablets daily (n=29)* *3) Vitamin D3 800 IU given as 2 tablets daily (n= 35)* *4) No tablets Randomised (n=35)* In a blinded or open-label way	• **ALLOCATION CONCEALMENT**: Inadequate (between blinded design or open trial design) • **RANDOMISATION:** Adequate • **BLINDING:** Some participants UNBLINDED • **FOLLOW-UP:** • Lost-to follow-up: 21 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding, study medication provided by Shire Pharmaceuticals • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : study run in the context of the RECORD trial (2005) • Object of the study was comparing recruitment and adherence between open trial design and RCT

Glendenning 2012[48] Design: RCT PL DB Duration of follow-up: 9 months	**Inclusion criteria:** living independently ambulant women registered with a general practitioner **Exclusion criteria:** consumption of vitamin D supplements either in isolation or as part of combination treatment like Actonel combi + D or Fosamax+ MiniMental State Score < 24 Investigators' opinion unsuitable for study	N = 686 **Mean age:** 76.7 +-4.1 y **Gender distribution:** 100% women **Vitamin D status at baseline:** average: 65.8 ± 22.7 nmol/l by automated Liaison method (Diasorin) **Bone status (osteoporosis, previous fractures? BMD?)** Data on previous falls, not fractures **Dietary calcium intake?** Average: 864+-412 mg/d Subjects were given written recommendations to consume 1300 mg/day Concomitant medication? unknown	*1) 150,000 IU cholecalciferol every 3 months (n=353)* *2) Placebo (n= 333)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION: Adequate** • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 9 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks:** ◦ main outcome was falls (OR vit D3/placebo = 1.1 (95% CI 0.80 - 1.56)) ◦ Fracture data obtained by Cochrane group from researcher ◦ Sample size calculation available

Harwood 2004[49] Design: R No PL Duration of follow-up: 1 year	**Inclusion criteria:** within 7 days of surgery for hip fracture, community residence independent in activities of daily living **Exclusion criteria:** Disease exclusions: institutionalised, diseases known to affect bone metabolism abbreviated mental test score < 7 at time of recruitment Drug exclusions: medications know to affect bone metabolism	N = 150 **Mean age:** 81,2 y **Gender distribution:** 100% women **Vitamin D status at baseline:** measured by radio-immunoassay mean: 29 nmol/l (6-85nmol/l) **Bone status (osteoporosis, previous fractures? BMD?)** all subjects recruited after operation for hip fracture **Dietary calcium intake?** No data **Concomitant medication?** No data	*1) Vitamin D2 300,000 IU by injection once at beginning of trial (n= 38)* *2) Vitamin D2 300,000 IU by injection once at beginning of trial and calcium 1000 mg daily as 2 tablets (n= 36)* *3) Vitamin D3 800 IU and calcium 1000 mg daily as 2 tablets (n= 39),* *4) No trial treatment (n=37)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Inadequate, no placebo's • **FOLLOW-UP:** • Lost-to follow-up: 20,6 % • Described: yes • Balanced across groups: yes • **ITT:** yes/no (‘author’s definition’) • **FUNDING**: Provalis health care**, industry** • **SELECTIVE REPORTING:** no • **Other important methodological remarks** study wasn't blinded, no placebo's very low number of events for falls (n=11)

Law 2006[50] Design: RT No PL Duration of follow-up: Median 10 months (interquartile: 7 - 14 months)	**Inclusion criteria:** living in a residential care home 60 years and over **Exclusion criteria:** temporary residents admitted for respite care already taking calcium / vitamin D or other drugs to increase bone density sarcoidosis, malignancy or other life-threatening illnesses	N = 3717 Mean age: 85 years Gender distribution: 86,8% women Vitamin D status at baseline: Measured by ELISA in 1% of subjects. Mean : 47nmol/l 25(OH)D Bone status (osteoporosis, previous fractures? BMD?) no data Dietary calcium intake? No data Concomitant medication? No data	*1) Ergocalciferol (vitamin D2) 2.5 mg every 3 months (1100 IU/d) (n=1762)* *2) No treatment (n= 1955)*	• **ALLOCATION CONCEALMENT**:Unclear • **RANDOMISATION:** Unclear, mentions "cluster randomised" • **BLINDING:** Inadequate, no placebo • **FOLLOW-UP:** • Lost-to follow-up: 2% • Described: no • Balanced across groups: unclear • **ITT:** yes • **FUNDING**: Sir Jules Thorn Charitable Foundation • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** no placebo • **Main finding**: incidence of fractures or falls was not lower in the vitamin D group

Lips 1996[51] Design: RCT DB PL Duration of follow-up: 3 years extension to 3,5 years for some	Inclusion criteria: reasonably healthy both community-dwelling and institutionalised patients **Exclusion criteria:** history of hip arthroplasty known hypercalcaemia history of hip fracture	N = 2578 **Mean age**: 80 ± 6 years Gender distribution: 1916 women (76%), 662 men **Vitamin D status at baseline:** measured in a subset Placebo group: 26nmol/l (25th-75th perc: 19-37) Vit D group: 27nmol/l (25th-75th perc: 19-36) **Bone status (osteoporosis, previous fractures? BMD?)** unknown **Dietary calcium intake?** Mean: 868mg/d semi-quantitatively assessed by questionnaire in a subset **Concomitant medication?** - Prescription habits of GP not modified, so additional Ca or Vit D possible - patients who used medication that influence bone metabolism were not excluded	*1) Vitamin D3 400 IU daily in a single tablet (n=1291)* *2) Identical placebo daily as a single tablet (n= 1287)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 37% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • Main finding: No decrease in incidence of hip fracture or other peripheral fractures after vitamin D supplementation

Lyons 2007[52] Design: RCT DB PL Duration of follow-up: 3 years	**Inclusion criteria:** resident in participating residential or nursing homes/sheltered housing; regardless of cognitive, visual, hearing or communication impairment **Exclusion criteria:** already taking 400 IU or more vitamin D/d known contraindication to vitamin D	N = 3440 **Mean age:** 84 years **Gender distribution:** 2624 women (76%), 816 men **Vitamin D status at baseline:** no data, no measurements **Bone status (osteoporosis, previous fractures? BMD?)** no data **Dietary calcium intake?** No data **Concomitant medication?** No data	*1) Ergocalciferol (vitamin D2) 2.5 mg (100,000 IU) every 4 months as two tablets (822 IU/d).* *(n= 1725)* *2) Two matching placebo tablets every 4 months.* *(n= 1715)*	• **ALLOCATION CONCEALMENT**:Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: **47 %** • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • Main finding: No evidence that four-monthly supplementation with 100,000 IU vit D2 is sufficient to substantially affect fracture incidence rate

Meyer 2002[53] Design: RCT DB PL Duration of follow-up: 2 years	**Inclusion criteria:** life expectancy > 6 months not permanently bedridden not having difficulties taking medicine Institutionalised patients from nursing homes **Exclusion criteria:** Disease exclusion: none given Drug exclusions: vitamin D supplementation of > 10 µg/day	N = 1144 **Mean age:** 84,7 ± 7.4 years **Gender distribution:** 868 women (75%), 276 men **Vitamin D status at baseline:** measured in a subsample mean placebo group: 51 ± 33 nmol/l intervention group: 47 ± 26nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** 28,6% previous fracture in control group, 26,4% previous fracture in the intervention group **Dietary calcium intake?** Mean intake: Placebo group: 446 +-196mg/d Mean intake Intervention group: 456+-196mg/d **Concomitant medication?** No data	*1) Cod liver oil 5 mL with vitamin D3* *2.2 µg/mL* *(equivalent to 400 IU)* *(n = 569)* *2) Cod liver oil 5 mL with vitamin D3* *0.1 to 0.2 µg/mL (control)* *(n=575)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Inadequate, states "days of the month (1-31 days) were divided randomly into group A and group B" • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up and drop-out: 37,5 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no, but reports pre-planned subgroup analyses • **Other methodological remarks**: power calculation available • Main finding: no difference in the incidence of hip fracture or other non-vertebral fractures

Mitri 2011[54] Design: RCT DB PL Duration of follow-up: 16 weeks treatment	**Inclusion criteria:** community-based ambulatory patients ≥ 40 years of age BMI (kg/m2) ≥ 25 (≥ 23 if Asian) with glucose intolerance or early diabetes, defined as a fasting plasma glucose concentration ≥ 100 mg/dL or 2-h glucose concentration ≥140 mg/dL after 75 g oral dextrose or glycated haemoglobin (Hb A1c) ≥ 5.8% **Exclusion criteria:** BMI > 40, Hb A1c > 7%, self-reported diabetes treated with pharmacotherapy weight change > 4 kg over the previous 6 months use of supplements that contained vitamin D or calcium in ≤ 8 weeks of screening and an unwillingness to discontinue supplementation for ≥ 2 weeks before the study initiation and during the study hyperparathyroidism, hypercalcemia, nephrolithiasis, chronic kidney disease conditions that may have affected vitamin D or calcium metabolism (eg, sarcoidosis) regular visits to tanning booths	N = 92 **Mean age:** 57 years **Gender distribution:** 47 women (51%), 45 men **Vitamin D status at baseline:** measured by liquid chromatography-mass spectrometry mean : 24,5 ± 0,8 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** unknown **Dietary calcium intake?** Estimated by food frequency questionnaire 859 +- 49 mg/d **Concomitant medication?** Exclusion of diabetes medication	*1) 2000 IU vitamin D3 and 800 mg calcium (as 2 doses calcium carbonate) daily (n=23)* *2) 2000 IU vitamin D3 and 2 placebos daily (n=23)* *3) 800 mg calcium (as calcium carbonate) and 1 placebo daily (n=22)* *4) Matching placebos (n=24)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Unclear • **FOLLOW-UP:** • Lost-to follow-up: 4,3% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Main objective of the study** was evaluating the effects of vitamin D and calcium supplementation on pancreatic β-cells, insulin sensitivity and glucose tolerance

Peacock 2000[41] Design: RCT DB PL Duration of follow-up: 4 years	**Inclusion criteria:** independently mobile over 60 60% community-dwelling, 40% institutionalised **Exclusion criteria:** terminal illness; Paget's disease of bone; recurrent urinary stone disease having been treated with sodium fluoride, bisphosphonate, steroids,or dilantin; having had renal disease requiring specific treatment; being excluded by primary physician	N = 438 **Mean age:** women: 73,7 years men: 75,9 years **Gender distribution:** 72 % women 28 % men **Vitamin D status at baseline:** median serum 25OH vitamin D3: 59 nmol/L by radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** both subjects with and without a previous fracture **Calcium intake monitoring?** baseline median calcium intake:546 mg/day **Concomitant medication:** ERT was not a reason for exclusion	*1) 750 mg calcium (n=135)* *2) 600 IU (15 µg 25OH) vitamin D3 (n=132)* *3) placebo (n=135)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate, randomized to strata by age, sex, serum 25(OH)D concentration and calcium intake • **BLINDING:** Participants: Adequate personnel/assessors: Unclear • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 33% of men, 41% of women • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING:** neutral funding • **SELECTIVE REPORTING:** no, but analysis on pre-specified subgroup (men vs women) • **Other important methodological remarks** Study's first objective was to detected changes to BMD

The RECORD trial group/ Grant 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months	**Inclusion criteria:** osteoporotic fracture in the previous 10 years **Exclusion criteria:** bed or chair-bound before fracture cognitive impairment cancer in the past 10 years with risk of bone metastasis fracture associated with bone abnormality hypercalcaemia renal stone in the past 10 years life expectancy less than 6 months individuals known to be leaving the UK daily intake of more than 200 IU vit D or more than 500 mg of Ca supplements intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** measured in a subgroup by straight-phase HPLC mean: 15.2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*1) 800 IU vit D3 (n=1343)* *2) 800 IU vit D3 & 1000 mg Ca as ca carbonte (n=1306)* *3) 1000 mg Ca as calcium carbonate (n= 1311)* *4) Placebo (n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no

Smith 2007[55] Design: RCT DB PL Duration of follow-up: 3 years	**Inclusion criteria:** aged 75 years and older, consenting and presenting for influenza vaccination at general practice **Exclusion criteria:** Disease exclusions: history of renal failure, renal stones, hypercalcaemia, sarcoidosis,current cancer, bilateral hip replacement, any history of treated osteoporosis Drug exclusions: taking 400 IU or more vitamin D daily	N = 9440 **Mean age:** 79.1 years **Gender distribution** 5086 women (54%), 4354 men (46%) **Vitamin D status at baseline**: analysed by radio-immunoassay mean concentration at baseline: 56.5 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** 38% of participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed in a subset by interviewer-administrated questionnaire Mean intake: 625 mg/day **Concomitant medication:** no data	*1) 300,000 IU intramuscular vit D2 injection* *(n = 4727)* *2) matching placebo* *(n = 4713)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no • **Other methodological remarks**: power calculation available • **Main finding**: ◦ No effect on falls (HR = 0.98 (95% CI 0.93 - 1.04)) ◦ No effect on fracture ◦ Small but significant excess of hip fracture risk associated with allocation to vitamin D amongst women

Trivedi 2003[56] Design: RCT Duration of follow-up: 5 years	**Inclusion criteria:** age 65 to 85 years living in the community from British doctors' study register and general practice register in Ipswich **Exclusion criteria**: Disease exclusions: contraindications to vitamin D supplementation e.g. renal stones, sarcoidosis, malignancy Drug exclusions: already taking vitamin D supplements	N = 2686 **Mean age**: 75 years **Gender distribution:** 2037 men (75,8%) and 649 women **Vitamin D status at baseline:** not measured **Bone status (osteoporosis, previous fractures? BMD?)** not reported **Dietary calcium intake?** Mean: 742 mg / day **Concomitant medication?** Some reported: steroids history of diseases reported	*One capsule 4-monthly of:* *1) Vitamin D3 100,000 IU (n=1345)* *2) Placebo (n=1341)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate, stratified by age and sex • **BLINDING:** Adequate participants and investigators • **FOLLOW-UP:** • Lost-to follow-up: 23,5 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no company funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks:** Compliance measured: 76% had 80% compliance, no difference between groups • **Main findings** • Fractures: RR = 0.78 (0.61-0.99) favors Vit D • Mortality: no significant difference

Vital D (Sanders) 2010[57] Design: RCT PL Duration of follow-up: 3 to 5 years	**Inclusion criteria:** women 70 years or older at higher risk of hip fracture (maternal hip fracture, past fracture, self-reported faller) **Exclusion criteria:** could not provide informed consent or information about falls or fractures residing permanently at a high-level care facility albumin corrected calcium level higher than 2.65 mmol/L creatinine level higher than 150 µmol/L currently taking vitamin D doses of 400 IU or more, calcitriol, or antifracture therapy	N = 2258 **Mean age**: 76 years **Gender distribution:** 100% women **Vitamin D status at baseline:** Serum 25(OH)vit D measured on a subset Intervention group: 53 nmol/l Placebo group: 45 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** both with and without previous fracture, but subjects at high risk of fracture **Dietary calcium intake?** Assessed by questionnaire, patients shown stratified **Concomitant medication?** No data	*1) 500 000 IU cholecalciferol each year (n = 1131)* *2) Placebo (n= 1125)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 10% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • Power calculation • Ca-intake subgroups **Main outcome** RR for falling = 1.15 (1.02 – 1.30) favours placebo RR for fracture = 1.26 (1.00 – 1.59) favours placebo

Witham 2010[58] Design: RCT DB Duration of follow-up: 20 weeks	**Inclusion criteria:** systolic heart failure vitamin D insufficiency (25(OH)D levels < 50 nmol/L) aged ≥ 70 years **Exclusion criteria:** a clinical diagnosis of osteomalacia, under investigation for recurrent falls taking vitamin D supplements moderate to severe cognitive impairment (defined as a Folstein mini-mental state examination < 15/30) serum creatinine > 200 µmol/L, liver function tests (bilirubin, alanine aminotransferase, and alkaline phosphatase) > 3 times the upper limit of the local reference range systolic blood pressure < 90 mmHg albumin-adjusted calcium (> 2.55 mmol/L or < 2.20 mmol/L) metastatic malignancy wheelchair-bound	N = 105 **Mean age**: 80 years **Gender distribution**: 69 men (66%), 36 women (33%) **Vitamin D status at baseline:** Serum 25(OH)D measured by radio-immunoassay mean: 22.1 nmol/l Bone status (osteoporosis, previous fractures? BMD?) no data Dietary calcium intake? No data Concomitant medication? Information on cardiovascular drugs used	*1) 100 000 IU of oral vitamin D2 at week 0 and week 10 (n=53)* *2) Placebo (n= 52)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and exclusions: 8,6 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** : information on fractures obtained through the author

Witham 2013[59] Design: RCT Duration of follow-up: 12 months	**Inclusion criteria:** community-dwelling participants 70 years and over serum 25(OH)D level < 75 nmol/L office systolic blood pressure > 140 mmHg **Exclusion criteria:** diastolic blood pressure > 90 mmHg systolic blood pressure > 180 mmHg hypertension known to be due to a correctable underlying medical or surgical cause estimated glomerular filtration rate < 40 mL/minute any liver function test (alanine aminotransferase, bilirubin, alkaline phosphatase) > 3 x upper limit of local normal range albumin-adjusted serum calcium > 2.60 mmol/L or < 2.15 mmol/l known metastatic malignancy or sarcoidosis, a history of renal calculi diagnosis of heart failure with left ventricular systolic dysfunction atrial fibrillation already taking vitamin D supplements	N = 159 **Mean age**: 77 years **Gender distribution**: 82 men (52%), 77 women (48%) **Vitamin D status at baseline:** See inclusion criteria **Bone status (osteoporosis, previous fractures? BMD?)** no data **Dietary calcium intake?** No data **Concomitant medication?** No data	*100,000 IU vitamin D3 every 3 months for 9 months* *(4 doses)* *(n= 80)* *vs* *Matching placebo every 3 months for 9 months* *(n= 79)*	• **ALLOCATION CONCEALMENT**: A • **RANDOMISATION:** A • **BLINDING: A** • **FOLLOW-UP:** • Lost-to follow-up, drop-out and exclusions: 10.7 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • Other important methodological remarks: ◦ main objective of the study was measuring an effect on blood pressure and other cardiovascular markers

Table 32: characteristics studies included in above-mentioned meta-analysis, from evidence profile

5.2.3 Summary and conclusions. Vitamin D versus placebo

Vitamin D versus placebo			
Bibliography: meta-analysis AVENELL 2014[2]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fractures, hip *Mixed primary and secondary prevention*	27,693 (15 studies)	RR= 1.12 [0.98 – 1.29] *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1, pooled results also contain trials with unhabitual vitamin D regimens (500,000IU once a year for Vital D 2010; 300,000 IU 4-monthly for Trivedi2003; together around 20% of pts.) that reported a heightened fracture risk Directness: -1 for differences in study population characteristics and different interventions. Imprecision: OK
Fractures, hip *secondary prevention*	2820 (3 studies)	RR= 1.08 [0.72 - 1.62] *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in study populations and interventions. Imprecision: OK
Fractures, all *Mixed primary and secondary prevention*	28,271 (15 studies)	RR = 1.03 [0.96 – 1.11] *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: -1pooled results also contain trials with unhabitual vitamin D regimens (500,000IU once a year for Vital D 2010; 300,000 IU 4-monthly for Trivedi2003; together around 20% of pts.) that reported a heightened fracture risk Directness: -1 for differences in study population characteristics and different interventions. Imprecision: OK
Fractures, all *Secondary prevention*	2820 (3 studies)	RR = 1.01 [0.84 – 1.21] *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in study populations and interventions. Imprecision: OK

Table 33: summary and conclusions

The Cochrane meta-analysis by Avenell et all. 2014[2] provides a large number of trials comparing several forms of vitamin D with placebo. Those forms are vitamin D3 but also vitamin D2 oral and injections. This is a problem for directness. Study populations are also diverse. Findings however are consistent between trials.

Treatment with vitamin D alone does not significantly reduce the risk of hip fractures.
Grade: LOW quality of evidence

Treatment with vitamin D alone does not significantly reduce the risk of hip fractures in people having already suffered a previous fracture.
Grade: MODERATE quality of evidence

Treatment with vitamin D alone does not significantly reduce the risk of any type of fracture.
Grade: LOW quality of evidence

Treatment with vitamin D alone does not significantly reduce the risk of any type of fracture in people having already suffered a previous fracture
Grade: MODERATE quality of evidence

5.3 Vitamin D3 versus calcium

In this chapter we present the results from interventions with only vitamin D3 compared with calcium, as well as sub-group analyses for primary and / or secondary prevention. Even though the result for the subgroup was not significant, we felt that those results could be of influence for the recommendations.

Data is extracted from the Cochrane-group meta-analysis by Avenell et al. 2014[2] (see section 5.2) A search was conducted for new RCT's, starting after the search date of the meta-analysis. No additional studies were identified.

5.3.1 Clinical evidence profile: vitamin D versus calcium

Ref	**Comparison:**	**Results**		
Avenell 2014[2]	**Vit D versus Calcium**	**Intervention Vit D** Mean (SD) or event rate	**Control Calcium** Mean (SD) or event rate	**RR (95% CI)**
Fractures, hip *secondary prevention only*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2, n = 2718)		RR=0.90 [0.61 – 1.32] *NS*
		47/1378	51/1340	
Non-vertebral fractures *mixed primary and secondary prevention*				
Avenell 2004[47], Mitri 2011[54], Peacock 2000[41], RECORD 2005[43]		Total (N = 4, n = 3021)		RR=1.10 [0.91-1.33] *NS*
		202/1533	178/1488	
Non-vertebral fractures *secondary prevention*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2, n = 2718)		RR=1.09 [0.90-1.32] *NS*
		187/1378	10/1466	
Vertebral fractures, *mixed primary and secondary prevention*				
Avenell 2004[47], Peacock 2000[41] RECORD 2005[43]		Total (N = 3, n = 2976)		RR= 2.21 [1.08-4.53] *NS*
		23/1510	3/1340	
Vertebral fractures, *secondary prevention*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2, n = 2718)		RR =1.30 [0.29 – 5.80] *NS*
		4/1378	3/1340	

Table 34: calcium versus vitamin D evidence profile

5.3.2 Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Avenell 2004[47] Design: part RCT part open design PL ((partially, study evaluates differences between open label and placebo controlled) Duration of follow-up: 46 months	**<u>Inclusion criteria:</u>** - osteoporotic fracture within the last 10 years - aged 70 years or older **<u>Exclusion criteria:</u>** - Disease exclusion: bed- or chair-bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of < 7, suffered from cancer likely to metastasise to bone within the previous 10 years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy < 6 months, known to be leaving the UK - Drug exclusions: taking more than 200 IU (5 µg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, HRT, selective oestrogen receptor modulators, or any vitamin D metabolite (such as calcitriol) in the last 5 years; vitamin D by injection in the last year	N = 134 (open design) **Mean age**: 78 years **Gender distribution:** 111 women = 111 (82.8%) , men = 23 (17.2%) **Vitamin D status at baseline:** unknown **Bone status:** previous osteoporotic fracture in the last 10 years **Dietary calcium intake?** No data **Concomitant medication?** No data	*1) Calcium 1000 mg and vitamin D3 800 IU given as 2 tablets daily* *(n=35)* *2) Calcium 1000 mg given as 2 tablets daily* *(n=29)* *3) Vitamin D3 800 IU given as 2 tablets daily* *(n= 35)* *4) No tablets* *Randomised (n=35)* In a blinded or open-label way	• **ALLOCATION CONCEALMENT**: Inadequate (between blinded design or open trial design) • **RANDOMISATION:** Adequate • **BLINDING:** Some participants UNBLINDED • **FOLLOW-UP:** • Lost-to follow-up: 21 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding, study medication provided by Shire Pharmaceuticals • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : study run in the context of the RECORD trial (2005) • Object of the study was comparing recruitment and adherence between open trial design and RCT

Mitri 2011[54] Design: RCT DB PL Duration of follow-up: 16 weeks treatment	**Inclusion criteria:** - community-based - ambulatory patients - ≥ 40 years of age - BMI (kg/m2) ≥ 25 (≥ 23 if Asian) - with glucose intolerance or early diabetes, defined as a fasting plasma glucose concentration ≥ 100 mg/dL or 2-h glucose concentration ≥140 mg/dL after 75 g oral dextrose or glycated haemoglobin (Hb A1c) ≥ 5.8% **Exclusion criteria:** - BMI > 40, - Hb A1c > 7%, - self-reported diabetes treated with pharmacotherapy - weight change > 4 kg over the previous 6 months - use of supplements that contained vitamin D or calcium in ≤ 8 weeks of screening and an unwillingness to discontinue supplementation for ≥ 2 weeks before the study initiation and during the study - hyperparathyroidism, hypercalcemia, nephrolithiasis, chronic kidney disease -conditions that may have affected vitamin D or calcium metabolism (eg, sarcoidosis) - regular visits to tanning booths	N = 92 **Mean age:** 57 years **Gender distribution:** 47 women (51%), 45 men **Vitamin D status at baseline:** measured by liquid chromatography-mass spectrometry mean : 24,5 ± 0,8 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** unknown **Dietary calcium intake?** Estimated by food frequency questionnaire mean: 859 +- 49 mg/d **Concomitant medication?** Exclusion of diabetes medication	*1) 2000 IU vitamin D3 and 800 mg calcium (as 2 doses calcium carbonate) daily* *(n=23)* *2) 2000 IU vitamin D3 and 2 placebos daily* *(n=23)* *3) 800 mg calcium (as calcium carbonate) and 1 placebo daily* *(n=22)* *4) Matching placebos* *(n=24)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Unclear • **FOLLOW-UP:** • Lost-to follow-up: 4,3% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Main objective of the study** was evaluating the effects of vitamin D and calcium supplementation on pancreatic β-cells, insulin sensitivity and glucose tolerance

Peacock 2000[41] Design: RCT DB PL Duration of follow-up: 4 years	**Inclusion criteria:** - independently mobile - over 60 - 60% community-dwelling, 40% institutionalised **Exclusion criteria:** - terminal illness; Paget's disease of bone; recurrent urinary stone disease - having been treated with sodium fluoride, bisphosphonate, steroids,or dilantin; - having had renal disease requiring specific treatment; - being excluded by primary physician	N = 438 **Mean age:** women: 73,7 years men: 75,9 years **Gender distribution:** 72 % women 28 % men **Vitamin D status at baseline:** median serum 25OH vitamin D3: 59 nmol/L radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** both subjects with and without a previous fracture **Calcium intake monitoring?** baseline median calcium intake:546 mg/day **Concomitant medication:** HRT was not a reason for exclusion	*1) 750 mg calcium (n=135)* *2) 600 IU (15 µg 25OH) vitamin D3 (n=132)* *3) placebo (n=135)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate, randomized to strata by age, sex, serum 25(OH)D concentration and calcium intake • **BLINDING:** Participants: Adequate • personnel/assessors: Unclear • • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 33% of men, 41% of women • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING:** neutral funding • **SELECTIVE REPORTING:** no, but analysis on pre-specified subgroup (men vs women) • **Other important methodological remarks** • Study's first objective was to detected changes to BMD • •

The RECORD trial group Grant 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months	**Inclusion criteria:** - osteoporotic fracture in the previous 10 years **Exclusion criteria:** - bed or chair-bound before fracture - cognitive impairment - cancer in the past 10 years with risk of bone metastasis - fracture associated with bone abnormality - hypercalcaemia - renal stone in the past 10 years - life expectancy less than 6 months - individuals known to be leaving the UK - daily intake of more than 200 IU vit D or more than 500 mg of Ca supplements - intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** measured in a subgroup by straight-phase HPLC mean: 15.2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*1) 800 IU vit D3 (n=1343)* *2) 800 IU vit D3 & 1000 mg Ca as calcium carbonate (n=1306)* *3) 1000 mg Ca as calcium carbonate (n= 1311)* *4) Placebo (n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no

Table 35: characteristics of studies included in above-mentioned meta-analysis from evidence profile

5.3.3. Summary and conclusions. Vitamin D versus calcium

Vitamin D versus calcium			
Bibliography: meta-analysis AVENELL 2014[2]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fractures, hip *secondary prevention*	2718 (2 studies)	RR = 0.90 [0.61 – 1.32] *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA, Avenell 2004 is a study embedded within RECORD 2005 and number of patients from Avenell (130) much lower than number from RECORD (over 5000 patients) Directness: OK Imprecision: OK
Fractures, non-vertebral *mixed primary and secondary prevention*	3021 (4 studies)	RR= 1.10 [0.91 – 1.33] *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 Imprecision: OK
Fractures, non-vertebral *secondary prevention*	2718 (2 studies)	RR = 1.09 [0.90 – 1.32] *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: NA Directness: -1 Imprecision: OK
Vertebral fractures	2976 (3 studies)	RR = 2.21 [1.08 – 4.53] *NS*	⊕⊖⊖⊖ **VERY LOW** Study quality: OK Consistency: -1 Directness: -1 Imprecision: -1 (sparse data, low number of events)
Vertebral fractures, *Secondary prevention*	2718 (2 studies)	RR = 1.30 [0.29 – 5.80] *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: NA Directness: -1 Imprecision: -1

Table 36: summary calcium versus vitamin D

The 2014 Cochrane meta-analysis by Avenell provides 4 trials comparing the effect of vitamin D alone on fractures, compared to treatment with calcium.
No data available on primary prevention of hip fractures with vitamin D compared to treatment with calcium.

Treatment with vitamin D alone, compared to treatment with calcium, does not significantly

reduce the risk of hip fractures in people having already suffered a previous fracture.
Grade: MODERATE quality of evidence

Treatment with vitamin D alone, compared to treatment with calcium, does not significantly reduce the risk of non-vertebral fractures.
Grade: MODERATE quality of evidence

Treatment with vitamin D alone, compared to treatment with calcium, does not significantly reduce the risk of non-vertebral fractures in people having already suffered a previous fracture.
Grade: LOW quality of evidence

Treatment with vitamin D alone, compared to treatment with calcium, heightens the risk of vertebral fractures.
Grade: VERY LOW quality of evidence

Treatment with vitamin D alone, compared to treatment with calcium, does not significantly reduce the risk of vertebral fractures in people having already suffered a previous fracture.
Grade: LOW quality of evidence

5.4 Vitamin D plus Calcium versus placebo or no treatment

In this chapter we present the results from interventions with vitamin D3 and calcium together, compared with placebo or no treatment.
We also present certain sub-group analyses even though the results for the subgroup was not always significant, but we felt that those could be of influence for the recommendations. This is the case for subgroup analyses of institutionalised or community-dwelling patients, and for the subgroups of patients with a history of previous fracture (secondary prevention) and those without selection based on previous fractures (not necessarily primary prevention, sometimes mixed primary/secondary population group).

Data is extracted from the 2014 Cochrane report by Avenell et al.[2] (see section 5.2)
An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies were found, however we found the proceedings of a new trial that is being conducted and that might deliver results in the future (Lopez-Torres et al. 2011[60])

5.4.1 Clinical evidence profile: vitamin D plus calcium versus placebo or no treatment

Ref	**Comparison:**	**Results**		
Avenell 2014[2]	**Vit D + Ca vs placebo**	**Intervention Vit D + Ca** Mean (SD) or event rate	**Control placebo** Mean (SD) or event rate	**RR (95% CI)**
Fractures, hip, *mixed primary and secondary prevention*				
Avenell 2004[47], Chapuy 1992[61], Chapuy 2002[62], Dawson-Hughes 1997[63], Harwood 2004[49], OSTPRE-FPS 2007[64], Porthouse 2005[65], RECORD 2005[43], WHI 2006[32]		Total (N = 9 , n = 49,853)		RR = 0.84 (0.74 – 0.96) SS
		399/24,709	461/25,144	
Fracutres, hip, *secondary prevention*				
Avenell 2004[47], Harwood 2004[49], Porthouse 2005[65], RECORD 2005[43]		Total (N = 4, n = 6134)		RR= 1.02 (0.71 – 1.47) *NS*
		56/2737	60/3397	
Fractures, hip, *institutionalized*				
Chapuy 1992[61], Chapuy 2002[62],		Total (N = 2, n = 3835)		RR = 0.75 (0.62 – 0.92) SS
		164/2023	199/1830	
Fractures, hip, *community-dwelling*				
Avenell 2004[47], Dawson-Hughes 1997[63], Harwood 2004[49], OSTPRE-FPS 2007[64], Porthouse 2005[65], RECORD 2005[43], WHI 2006[32]		Total (N = 7, n = 46,400)		RR = 0.91 (0.77 – 1.09) *NS*
		235 / 22,686	262 / 23,314	
Non-vertebral fractures, *mixed primary and secondary prevention*				
Avenell 2004[47], Bolton-Smith 2007[66], Chapuy 1992[61], Chapuy 2002[62], Dawson-Hughes 1997[63], Harwood 2004[49], OSTPRE-FPS 2007[64], RECORD 2005[43]		Total (N = 8 , n = 10,380)		RR = 0.86 (0.78 – 0.96) SS
		581 / 5274	638 / 5106	
Non-vertebral fractures, *secondary prevention*				
Avenell 2004[47], Harwood 2004[49], RECORD 2005[43]		Total (N = 3, n = 2820)		RR = 0.93 (0.77 – 1.13) NS
		173 / 1416	186 / 1404	

Vertebral fractures			
Avenell 2004[47], OSTPRE-FPS 2007[64], RECORD 2005[43], WHI 2006[32]	Total (N = 4, n = 42,185)		RR = 0.89 (0.74 – 1.09) NS
	190 / 21,103	212 / 21,082	
Vertebral fractures, *secondary prevention*			
Avenell 2004[47], RECORD 2005[43]	Total (N = 2, n = 2708)		RR = 0.34 (0.04 – 3.20) NS
	0/1341	2/1367	
Fractures, all, *mixed primary and secondary prevention*			
Avenell 2004[47], Bolton-Smith 2007[66], Chapuy 1992[61], Chapuy 2002[62], Dawson-Hughes 1997[63], Harwood 2004[49], OSTPRE-FPS 2007[64], Porthouse 2005[65], RECORD 2005[43], WHI 2006[32]	Total (N = 10, n = 49,976)		RR = 0.95 (0.90 – 0.99) SS
	2741 / 24,771	2889 / 25,205	
Fractures, all, *secondary prevention*			
Avenell 2004[47], Harwood 2004[49], Porthouse 2005[65], RECORD 2005[43]	Total (N = 4, n = 6134)		RR = 0.93 (0.79 – 1.10) NS
	231 / 2737	279 / 3397	
Fractures, all, *institutionalized*			
Chapuy 1992[61], Chapuy 2002[62]	Total (N = 2, n = 3853)		RR = 0.85 (0.74 – 0.98) SS
	324 / 2023	342 / 1830	
Fractures, all, *community-dwelling*			
Avenell 2004[47], Bolton-Smith 2007[66], Dawson-Hughes 1997[63], Harwood 2004[49], OSTPRE-FPS 2007[64], Porthouse 2005[65], RECORD 2005[43], WHI 2006[32]	Total (N = 8, n = 46,123)		RR = 0.96 (0.91 – 1.01) NS
	2417 / 22748	2547 / 23375	

Table 37: clinical evidence profile: calcium plus vitamin D versus placebo

5.4.2. Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria Patient characteristics		Comparison	Study quality
Avenell 2004[47] Design: part RCT part open design PL (partially, study evaluates differences between open label and placebo controlled) Duration of follow-up: 46 months	**<u>Inclusion criteria:</u>** - osteoporotic fracture within the last 10 years - aged 70 years or older **<u>Exclusion criteria:</u>** - Disease exclusion: bed- or chair-bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of < 7, suffered from cancer likely to metastasise to bone within the previous 10 years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy < 6 months, known to be leaving the UK - Drug exclusions: taking more than 200 IU (5 µg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, HRT, selective oestrogen receptor modulators, or any vitamin D metabolite (such as calcitriol) in the last 5 years; vitamin D by injection in the last year	N = 134 (open design) **Mean age:** 78 years **Gender distribution**: women = 111 (82.8%) , men = 23 (17.2%) **Vitamin D status at baseline:** unknown **Bone status:** previous osteoporotic fracture in the last 10 years **Dietary calcium intake?** No data **Concomitant medication?** No data	*1) Calcium 1000 mg and vitamin D3 800 IU given as 2 tablets daily (n=35)* *2). Calcium 1000 mg given as 2 tablets daily (n=29)* *3) Vitamin D3 800 IU given as 2 tablets daily (n= 35)* *4) No tablets Randomised (n=35)* *In a blinded or open-label way*	• **ALLOCATION CONCEALMENT**: Inadequate • (between blinded design or open trial design) • **RANDOMISATION:** Adequate • **BLINDING:** Some participants UNBLINDED • **FOLLOW-UP:** • Lost-to follow-up: 21 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding, study medication provided by Shire Pharmaceuticals • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : study run in the context of the RECORD trial (2005) • Object of the study was comparing recruitment and adherence between open trial design and RCT

Chapuy 1992[61] Design: RCT DB Duration of follow-up: 18 months	**Inclusion criteria:** - Elderly women - Ambulant (walk indoors with a cane) - No serious medical condition - Life expectancy of at least 18 months **Institutionalised** **Exclusion criteria:** - Having received drugs known to alter bone metabolism (corticosteroids,thyroxine...) within the past year - Being treated with fluoride salts >3 months or having received Ca or vitamin D treatment during the previous six months or for more than one year the past five years	N = 3270 **Mean age:** 84 (69-106) **Gender distribution:** 100% women **Vitamin D status at baseline:** measured, not reported competitive binding-protein assay mean: 16 ± 11 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** women who had fractures in the past were not excluded **Calcium intake monitoring?** Semi-quantitative assessment mean: 512 mg / day **Concomitant medication:** women taking oestrogen or thiazide diuretic were not excluded	*1) 1200 mg elemental calcium (as tricalcium phosphte) + 800 IU vitamin D3* *(n = 1634)* *2) placebo* *(n = 1636)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear, states • "the women were randomly assigned to the treatment of the placebo group in groups of four at each nursing home" • **BLINDING:** Adequate • • **FOLLOW-UP:** • Deaths: 16 in vit D group; 17% in placebo group • Withdrawal for other reasons: 30% in vit D group; 29% in placebo group • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • • **Other important methodological remarks** • Vertebral fractures not measured

Chapuy 2002[62] Design: RCT DB Duration of follow-up: 2 years	**Inclusion criteria:** Ambulatory women **Institutionalized** (apartment homes for elderly) Life expectancy of 24 months **Exclusion criteria :** Disease exclusions: intestinal malabsorption, hypercalcaemia (serum calcium > 2.63 mmol/L), chronic renal failure (serum creatinine > 150 µmol/L) Drug exclusions: received drugs known to alter bonemetabolism, such as corticosteroids, anticonvulsants or a high dose of thyroxine, in the past year. Fluoride salts (> 3 months), bisphosphonates, calcitonin (> 1 month), calcium (> 500 mg daily), vitamin D (> 100 IU daily) in last 12 months	N = 583 **Mean age:** 85.2 y **Gender distribution:** 100% women **Vitamin D status at baseline:** Serum 25(OH)D measured by competitive-binding protein assay Mean: 9,2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** data on BMD given **Calcium intake monitoring?** Semi-quantitatively assessed by questionnaire, mean : 557 mg / day **Concomittant medication?** registered, data not given	*1) Calcium 1200 mg as tricalcium phosphate and vitamin D3 800 IU daily as 1 sachet* *2) Calcium 1200 mg as tricalcium phosphate sachet and 2 pills of vitamin D3 400 IU daily* *(groups 1 and 2: n = 389)* *3) 1 placebo sachet and 2 placebo tablets daily. (n = 194)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** • Participants: Adequate • personnel/assessors: Unclear • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 27.2% separate CA-VitD, 29.1 fixed Ca+vitD, 36.1% placebo • Described: y • Balanced across groups: no • **ITT:** yes • **FUNDING**: Merckx KGaA • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • Combines ca-vit D fixed and separate combination to evaluate global impact of calcium and vit D3 treatment because no biochemical parameter was different. • Not powered to detect a reduction in hip fracture rate

Dawson-Hughes 1997[63] Design: RCT Duration of follow-up: 3 years	**Inclusion criteria:** 65 years or older living at home **Exclusion criteria:** current cancer or hyperparathyroidism renal stone history within 5 years bilateral hip surgery femoral neck BMD more than 2 SD below the mean for age and gender dietary calcium intake exceeding 1500 mg/day laboratory evidence of renal or liver disease Drug exclusions: therapy with a bisphosphonate, calcitonin, oestrogen, tamoxifen, or testosterone in the past 6 months, or fluoride within the past 2 years	N = 445 **Mean age:** 71 **Gender distribution:** 176 men (45%) – 213 women (55%) **Vitamin D status at baseline:** serum 25(OH)D measured by competitive protein-binding method **Bone status (osteoporosis, previous fractures? BMD?)** BMD measurements given **Calcium intake monitoring?** Semi-quantitatively assessed by questionnaire Mean: 727 mg / day **Concomitant medication:** no data	*1) 500 mg elemental calcium plus vitamin D3 700 IU orally daily* *(n = 187)* *2) Double placebo* *(n = 202)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear, states "randomly assigned", no extra information • **BLINDING:** Adequate for participants, unclear for assessors • **FOLLOW-UP:** • Lost-to follow-up + Drop-out and Exclusions: 28.5% • Described: yes • Balanced across groups: not described • **ITT:** no • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : high compliance in both groups >90%, low number of events • **Main finding:** Significant reduction of the risk of any non-vertebral fractures (RR= 0.4 (95% CI 0.2 to 0.8, p=0.01))

Harwood 2004[49] Design: R No PL Duration of follow-up: 1 year	**Inclusion criteria:** within 7 days of surgery for hip fracture, community residence independent in activities of daily living **Exclusion criteria**: Disease exclusions: institutionalised, diseases known to affect bone metabolism abbreviated mental test score < 7 at time of recruitment Drug exclusions: medications know to affect bone metabolism	N = 150 **Mean age**: 81,2 y **Gender distribution**: 100% women **Vitamin D status at baseline**: measured by radio-immunoassay mean: 29 nmol/l (6-85nmol/l) **Bone status** (osteoporosis, previous fractures? BMD?) all subjects recruited after operation for hip fracture **Dietary calcium intake?** No data **Concomitant medication?** No data	*1. Vitamin D2 300,000 IU by injection once at beginning of trial* *(n= 38)* *2. Vitamin D2 300,000 IU by injection once at beginning of trial and calcium 1000 mg daily as 2 tablets* *(n= 36)* *3. Vitamin D3 800 IU and calcium 1000 mg daily as 2 tablets* *(n= 39),* *4. No trial treatment* *(n=37)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Inadequate, no placebo's • **FOLLOW-UP:** • Lost-to follow-up: 20,6 % • Described: yes • Balanced across groups: yes • **ITT:** yes/no ('author's definition') • **FUNDING**: Provalis health care**, industry** • **SELECTIVE REPORTING:** no • **Other important methodological remarks** study wasn't blinded, no placebo's • very low number of events for falls (n=11)

OSTPRE-FPS (Salovaara) 2007[64] Design: RCT No PL Open label Duration: 3 years	**Inclusion criteria:** women aged 65 to 71 years living in the northern savonia **Exclusion criteria:** taken part in any trials or BMD measurements of the OSTRPRE study	N = 3432 **Mean age:** 67 years **Gender distribution:** 100% women **Vitamin D status at baseline:** Measured by DiaSorin radioimmunoassay In a subsample of 350 women from each group Mean: 50 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** 35% had a previous fracture **Calcium intake monitoring?** Semi-quantitatively assessed by food frequency questionnaire Mean: 957 mg / day **Concomitant medication:** not reported	*1) 1000 mg of calcium as calcium carbonate* *+* *800 IU of cholecalciferol* *(n = 1586)* *2) no treatment* *(n = 1609)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Inadequate, OPEN LABEL • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 8,5% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding, tablets donated by Nycomed • **SELECTIVE REPORTING:** no • **Main finding:** non-significant decreased risk of fractures

Porthouse 2005[65] Design: RCT Open Duration of follow-up: 18 to 42 months median: 24	**Inclusion criteria:** women 70 or older one or more risk factors for hip fractures: any previous fracture, low body weight, smoker, family history of hip fracture, fair or poor self reported health living in nursing homes **Exclusion criteria:** Disease exclusions: kidney or bladder stones, renal failure, hypercalcaemia, cognitive impairment, life expectancy < 6 months Drug exclusions: current calcium supplementation of > 500 mg/day	N = 3314 **Mean age:** 77 ± 5 years **Gender distribution:** women 100% **Vitamin D status at baseline:** not measured **Bone status (osteoporosis, previous fractures? BMD?)** not measured **Calcium intake monitoring?** Not measured **Concomitant medication:** not reported	*1) 1000 mg calcium carbonate / day* *+* *800 IU / day of vitamin D3* *(n = 1321)* *2) placebo* *(n = 1993)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear, states "randomized" (control vs intervention 3 : 2) • **BLINDING:** open design • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: ◦ Intervention group: 33% ◦ Control group: 1.6% • Described: no • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding, company provided study medication • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • Pilot study undertaken: patients of pilot study included for analysis (n=117) • Relatively low adherence in intervention group after 18 months: 58.6%

The RECORD trial group /Grant 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months	**Inclusion criteria:** osteoporotic fracture in the previous 10 years **Exclusion criteria:** bed or chair-bound before fracture cognitive impairment cancer in the past 10 years with risk of bone metastasis fracture associated with bone abnormality hypercalcaemia renal stone in the past 10 years life expectancy less than 6 months individuals known to be leaving the UK daily intake of more than 200 IU vit D or more than 500 mg of Ca supplements intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** measured in a subgroup by straight-phase HPLC mean: 15.2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*1) 800 IU vit D3 (n=1343)* *2) 800 IU vit D3 & 1000 mg Ca as calcium carbonate (n=1306)* *3) 1000 mg Ca as calcium carbonte (n= 1311)* *4) matching placebos (n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no

WHI (Jackson) 2006[32] Design RCT Pl Duration: 7 years	**Inclusion criteria:** 50 to 79 years no medical condition associated with predicted survival of less than 3 years **Exclusion criteria:** Disease exclusions: hypercalcaemia, renal calculi Drug exclusions: corticosteroid use, calcitriol use, calcium supplements > 1000 mg/day, vitamin D > 600 IU/day (> 1000 IU/day after 1999)	N = 36,282 **Mean age:** 62,4 years **Gender distribution:** 100% women **Vitamin D status at baseline:** measured in case-control pairs matching for age, latitude, race and date of venipuncture by DiaSorin Liaison chemiluminescent immunoassay system **Bone status (osteoporosis, previous fractures? BMD?)** history of fractures recorded, approx. 10% had a fracture at age ≥ 55 **Calcium intake monitoring?** Food frequency questionnaire + intake of calcium from supplements **Concomitant medication:** 50% of patients under hormone replacement therapy 20,7% taking alendronate 1,8% taking risendronate 3,0% taking raloxifene 1,2% taking calcitonin	*1) 1000 mg calcium as calcium carbonate +* *400 IU vitamin D3* *as 2 tablets daily* *(n = 18176))* *2) 2 placebo tablets daily* *(n= 18106)*	• **ALLOCATION CONCEALMENT**:Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 2,7% • Drop-out and Exclusions: (deaths) 4,3 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** recruited among women already enrolled in the WHI dietary modification trial or WHI hormone therapy trial → HRT has an effect on bone + personal calcium supplements of up to 1000 mg / day and vit D supplements (up to 600 IU then 1000 iu / day) were also permitted

Table 38: characteristics of included studies from above-mentioned meta-analysis

5.4.3 Summary and conclusions. Vitamin D plus calcium versus placebo or no treatment

Vitamin D plus calcium versus placebo			
Bibliography: meta-analysis AVENELL 2014[2]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fractures, hip *mixed primary and secondary prevention*	49,853 (9)	RR = 0.84 (0.74 – 0.96) *SS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -2, differences in populations, interventions, plus large number of patients from WHI trial, with 50% under hormone replacement therapy and 20% under alendronate (excluded from other studies) Imprecision: OK
Fractures, hip *secondary prevention*	6134 (4)	RR= 1.02 (0.71 – 1.47) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in populations and interventions Imprecision: OK
Fractures, hip *institutionalized*	3835 (2)	RR = 0.75 (0.62 – 0.92) *SS*	⊕⊕⊕⊖ **MODERATE** Study quality: -1, unclear risks of bias, regrouping of study arms Consistency: OK Directness: OK Imprecision: OK
Fractures, hip *Community-dwelling*	46,400 (7)	RR = 0.91 (0.77 – 1.09) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -2, differences in populations, interventions, plus large number of patients from WHI trial, with 50% under hormone replacement therapy and 20% under alendronate (excluded from other studies) Imprecision: OK
Non-vertebral fractures *mixed primary and secondary prevention*	10,380 (8)	RR = 0.86 (0.78 – 0.96) *SS*	⊕⊕⊖⊖ **LOW** Study quality: -1, 3/8 unblinded, risk of bias unclear Consistency: OK Directness: -1 for differences in populations and interventions Imprecision: OK
Non-vertebral fractures, *secondary prevention*	2820 (3)	RR = 0.93 (0.77 – 1.13) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in populations and interventions Imprecision: OK

Vertebral fractures *mixed primary and secondary prevention*	42,185 (4)	RR = 0.89 (0.74 – 1.09) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -2, differences in populations, interventions, plus large number of patients from WHI trial, with 50% under hormone replacement therapy and 20% under alendronate (excluded from other studies) Imprecision: OK
Vertebral fractures, *Secondary prevention*	2708 (2)	RR = 0.34 (0.04 – 3.20) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: NA, Avenell 2004 is a trial embedded within RECORD 2005 and number of patients from Avenell (130) much lower than number from RECORD (over 5000 patients) Directness: OK Imprecision: -1, large CI
Fractures, all *mixed primary and secondary prevention*	49,976 (10)	RR = 0.95 (0.90 – 0.99) *SS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -2, differences in populations, interventions, plus large number of patients from WHI trial, with 50% under hormone replacement therapy and 20% under alendronate (excluded from other studies) Imprecision: OK
Fractures, all *secondary prevention*	6134 (4)	RR = 0.93 (0.79 – 1.10) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in populations and interventions Imprecision: OK
Fractures, all *institutionalised*	3853 (2)	RR = 0.85 (0.74 – 0.98) *SS*	⊕⊕⊕⊖ **MODERATE** Study quality: -1, unclear risks of bias, regrouping of study arms Consistency: OK Directness: OK Imprecision: OK
Fractures, all *community-dwelling*	46,123 (8)	RR = 0.96 (0.91 – 1.01) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: OK Directness: -2, differences populations, interventions, plus large number of patients from WHI trial, with 50% under hormone replacement therapy and 20% under alendronate (excluded from other studies) Imprecision: OK

Table 39: summary calcium and vitamin d versus placebo

The 2014 Cochrane meta-analysis by Avenell provides data on 10 trials investigating the effect of vitamin D and calcium on fractures, compared with placebo.
It should be noted that institutionalised patients typically form an older group (mean age >80).

Treatment with vitamin D plus calcium, compared to placebo, significantly reduces the risk of hip fractures in people with and without previous hip fractures

Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, significantly reduces the risk of hip fractures in people who had a previous hip fracture.
Grade: MODERATE quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, significantly reduces the risk of hip fractures in people living in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade: MODERATE quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does not significantly reduce the risk of hip fractures in people living in the community.
Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, significantly reduces the risk of non-vertebral fractures in people with and without a previous fracture.
Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does not significantly reduces the risk of non-vertebral fractures in people having already suffered a previous fracture.
Grade: MODERATE quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does not significantly reduce the risk of vertebral fractures in people with and without a previous fracture.
Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does not significantly reduce the risk of vertebral fractures in people having already suffered a previous fracture.
Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does significantly reduce the risk of having any fracture in people with and without a previous fracture.
Grade: LOW quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does significantly reduce the risk of having any fracture in people having already suffered a previous fracture.
Grade: MODERATE quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does significantly reduce the risk of having any fracture in people living in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade: MODERATE quality of evidence

Treatment with vitamin D plus calcium, compared to placebo, does not significantly reduce the risk of having any fracture in people living in the community.
Grade: LOW quality of evidence

5.5 Vitamin D plus Calcium versus Calcium

In this chapter we present the results from interventions with vitamin D3 and calcium together, compared with calcium alone.
We also present certain sub-group analyses even though the result for the subgroup was not significant, but we felt that those could be of influence for the recommendations.

Data is extracted from the 2014 Cochrane report by Avenell[2] (see section 5.2)
An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies were found.

Ref	**Comparison:**	**Results**		
Avenell 2014[2]	**Vit D + Calcium versus Calcium**	**Intervention Vit D + Calcium** Mean (SD) or event rate	**Control Calcium** Mean (SD) or event rate	**RR (95% CI)**
Fractures, hip, *mixed primary and secondary prevention*				
Avenell 2004[47], Bischoff 2003[67], Burleigh 2007[68], Garay Lillo 1997[69], Janssen 2010[70], Pfeifer 2000[71], RECORD 2005[43]		Total (N= 7 , n = 7411)		RR = 0.84 (0.63 - 1.13) *NS*
		79/3700	94/3711	
Fractures, hip *secondary prevention*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2 , n = 2681)		RR = 0.96 (0.65 – 1.41) *NS*
		48/1341	50/1340	
Non-vertebral fractures, *mixed primary and secondary prevention*				
Avenell 2004[47], Burleigh 2007[68], Janssen 2010[70], Komulainen 1998[72], Pfeifer 2000[71], RECORD 2005[43]		Total (N = 6, n = 3336)		RR = 0.96 (0.79 – 1.16) *NS*
		183 / 1668	191 / 1668	
Non-vertebral fractures *secondary prevention*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2 , n = 2681)		RR = 1.00 (0.82 – 1.22) *NS*
		167/1341	167/1340	
Vertebral fractures, *secondary prevention only*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2 , n = 2681)		RR = 0.14 (0.01 – 2.77) *NS*
		0/1341	3/1340	
Fractures, all , *mied primary and secondary prevention*				
Avenell 2004[47], Bischoff 2003[67], Burleigh 2007[68], Flicker 2005[73], Garay Lillo 1997[69], Janssen 2010[70], Komulainen 1998[72], Pfeifer 2000[71], Pfeifer 2009[74], Prince 2008[75], RECORD 2005[43]		Total (N = 11, n = 8812)		RR = 0.87 (0.74 - 1.02) *NS*
		248/4402	286/4410	
Fractures all, *secondary prevention*				
Avenell 2004[47], RECORD 2005[43]		Total (N = 2, n = 2681)		RR = 0.98 (0.80 – 1.20) *NS*
		167/1341	170 / 1340	

Table 40: clinical evidence profile calcium and vitamin D versus calcium

5.5.2. Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Avenell 2004[47] Design: part RCT part open design PL (partially, study evaluates differences between open label and placebo controlled) Duration of follow-up: 46 months	**<u>Inclusion criteria:</u>** - osteoporotic fracture within the last 10 years - aged 70 years or older **<u>Exclusion criteria:</u>** - Disease exclusion: bed- or chair-bound prior to fracture, cognitive impairment indicated by an abbreviated mental test score of < 7, suffered from cancer likely to metastasise to bone within the previous 10 years, fracture associated with pre-existing local bone abnormality, known hypercalcaemia, renal stone in the last 10 years, life expectancy < 6 months, known to be leaving the UK - Drug exclusions: taking more than 200 IU (5 µg) vitamin D or more than 500 mg calcium supplements daily; had fluoride, bisphosphonates, calcitonin, tibolone, HRT, selective oestrogen receptor modulators, or any vitamin D metabolite (such as calcitriol) in the last 5 years; vitamin D by injection in the last year	N = 134 (open design) **Mean age:** 78 years **Gender distribution**: women = 111 (82.8%) , men = 23 (17.2%) **Vitamin D status at baseline:** unknown **Bone status:** previous osteoporotic fracture in the last 10 years **Dietary calcium intake?** No data **Concomitant medication?** No data	*1. Calcium 1000 mg and vitamin D3 800 IU given as 2 tablets daily (n=35)* *2. Calcium 1000 mg given as 2 tablets daily (n=29)* *3. Vitamin D3 800 IU given as 2 tablets daily (n= 35)* *4. No tablets Randomised (n=35)* *In a blinded or open-label way*	• • **ALLOCATION CONCEALMENT**: Inadequate • (between blinded design or open trial design) • **RANDOMISATION:** Adequate • **BLINDING:** Some participants UNBLINDED • **FOLLOW-UP:** • Lost-to follow-up: 21 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding, study medication provided by Shire Pharmaceuticals • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : study run in the context of the RECORD trial (2005) • Object of the study was comparing recruitment and adherence between open trial design and RCT

Bischoff 2003[67] Design: RCT DB Duration of follow-up: 18 weeks	**Inclusion criteria:** - in long-stay geriatric care unit - 60 years or over, - ability to walk 3 meters with or without walking aid **Exclusion criteria:** Disease exclusions: primary hyperparathyroidism, hypocalcaemia, hypercalciuria, creatinine > 117 ìmol/L, fracture or stroke in last 3 months Drug exclusions: HRT, calcitonin, fluoride, bisphosphonates in last 24 months	N = 122 **Mean age**: 85.3 ± 6.6 years **Gender distribution:** 100% women **Vitamin D status at baseline:** serum 25-(OH)D measured by radio-immunoassay Cal group: 11.6 ng/ml Cal+vitD: 12.3 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** Previous fractures and falls recorded. Mixed primary and secondary prevention. **Dietary calcium intake?** Evaluated by dietician **Concomitant medication?** Some reported (benzodiazepines, diuretic use)	*1) 1200 mg Ca +800 IU vit D3 (n=62)* *2) 1200 mg Ca (n=60)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate, participants and assessors • **FOLLOW-UP:** • Lost-to follow-up: 27 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: Strathmann AG (industry) + other neutral sources • **SELECTIVE REPORTING:** no • **Other important remarks:** data on hip fractures was provided by dr. Bischoff via email • 12 week treatment period done within winter months • **Main finding:** 49% reduction of falls (95% CI: 14-71%; p<0.01))

Burleigh 2007[68] Design: RCT Duration of follow-up: median : 30 days	**<u>Inclusion criteria:</u>** - staying in a geriatric medical unit - >65 years **<u>Exclusion criteria:</u>** - known hypercalcaemia - urolithiasis - renal dialysis. - Terminally ill or bed-bound with reduced Glasgow Coma Score, – already prescribed calcium and vitamin D – nil by mouth at time of admission	N = 205 **Median age**: 84 **Gender distribution:** 121 women (59%), 84 men (41%) **Vitamin D status at baseline:** Serum 25(OH)D measured 1 in 4 subjects, median : 22 nmol/l by Nichols Advantage Analyser **Bone status (osteoporosis, previous fractures? BMD?)** Both patients with and without previous fractures **Dietary calcium intake?** unknown **Concomitant medication?** unknown	*1) 1200 mg / day Ca + 800 IU vit D3* *(n=101)* *2) 1200 mg of calcium* *(n=104)*	• **ALLOCATION CONCEALMENT**:A • **RANDOMISATION:** A • **BLINDING: A** • **FOLLOW-UP:** • Lost-to follow-up: 3% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**:undisclosed • **SELECTIVE REPORTING:** no • **Other important methodological remarks:** power calculation available, study is underpowered • **Main finding**: non-significant reduction of falls

Flicker 2005[73] Design: RCT Duration of follow-up: 2 years	**Inclusion criteria:** - Living in hotel or nursing home - Being vitamin D deficient **Exclusion criteria:** - Serum 25(OH)D levels above 90 nmol/l - Use of agents that could affect bone metabolism (warfarin, chronic heparin therapy, vitamin D therapy within previous 3 months), glucocorticoids at average dose of higher than 5 mg prednisolone for more than one month the previous year, current use of bisphosphonates, hormone replacement therapy - Thyrotoxicosis within the previous 3 years, primary hyperparathyroïdism treated within the previous 3 years, multiple myeloma, Paget's disease of bone, history of malabsorption, intercurrent active malignancy, other disorders affecting bone and mineral metabolism.	N = 625 **Mean age**: 83.4 ± 6.6 **Gender distribution:** 95% female **Vitamin D status at baseline:** serum 25(OH)D levels between 25 and 90 nmol/l measured by radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** Both patients with and without previous fractures **Dietary calcium intake?** unknown **Concomitant medication?** Allowed were: furosemide and / or thiazide diuretics	*1) 600 mg Calcium / day +10,000 IU vitamin D3 once a week, then switched to 1000 IU/day (n=313)* 2) 600 mg Ca/day (n=312)	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Participants/Personnel: acceptable but not adequate • **FOLLOW-UP:** • Lost-to follow-up: Drop out: after 1 year 22% (placebo), 24% (intervention) Drop out after 2 years: 42 % (PL), 41% (intervention) • Described: yes • Balanced across groups: yes • **ITT:** no, withdrawals and deaths excluded from analysis • **FUNDING**: neutral funding • **SELECTIVE REPORTING:** no • **Main finding:** significant reduction of incident ratio for falling in ITT (0.73 (95% CI: 0.57-0.95))

Garay Lillo (*) 1997[69] Design: Probably RCT Duration of follow-up: 2 years	**Inclusion criteria:** - ambulant community-living women - between 65 and 85 years of age **Exclusion criteria:** - Disease exclusions: abnormal renal function (serum creatinine > 144 µmol/L), serious medical problems, thyroid or parathyroid abnormalities, intestinal malabsorption, previous gastrectomy – Drug exclusions: administration of calcium or vitamin D in the previous 6 months; administration of corticosteroids, anticonvulsants, or thyroxine in the year prior to enrolment	N = 6945 **Mean age:** See (*) **Gender distribution:** 100% women **Vitamin D status at baseline:** See (*) **Bone status (osteoporosis, previous fractures? BMD?)** See (*) **Dietary calcium intake?** See (*) **Concomitant medication?** See (*)	*1. Tricalcium phosphate 1.2 g daily plus 25(OH)D 16,000 IU per week* *Randomised unclear, 2086 completed 1 year* *2. Tricalcium phosphate 1.2 g daily* *Randomised unclear, 2099 completed 1 year*	• **ALLOCATION CONCEALMENT**: U • **RANDOMISATION:** U • **BLINDING: U** • **FOLLOW-UP:** • Lost-to follow-up: 43.7 % • Described: unknown • Balanced across groups: unknown • **ITT:** unknown • **FUNDING**: unknown • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : (*) Article in Spanish, some data is reproduced from Avenell 2014 Cochrane report, but not all data was available to our researchers

Janssen 2010 Design: RCT Duration of follow-up: 6 months	**<u>Inclusion criteria:</u>** - >65 years - able to walk and follow simple instructions – serum 25(OH)D concentration between 20 nmol/L and 50 nmol/L **<u>Exclusion criteria:</u>** - treatment with vitamin D or steroids in the previous 6 months - history of hypercalcemia or renal stones - liver cirrhosis - serum creatinine > 200 µmol/ L - malabsorptive bowel syndrome - primary hyperparathyroidism or uncontrolled thyroid disease - anticonvulsant drug therapy, and/or presence of any other condition that would probably interfere with the patient's compliance (i.e. surgery planned)	N = 70 **Mean age:** Intervention group: 82.4 placebo group 79.2 **Gender distribution:** 100% women **Vitamin D status at baseline:** Serum 25(OH)D Intervention group: 32.6 nmol/l Placebo group: 34.3 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** unknown **Dietary calcium intake?** unknown **Concomitant medication?** unknown	*1) 400 IU vit D3 / day + 500 mg/day Calcium (n=36)* *2) 500 mg / day calcium (n= 34)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 15.7% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: neutral • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : - most women were institutionalised (residential homes for the elderly) - even though randomized independently, the two groups were not completely comparable - data on fractures provided by author, not reported in article

Komulainen 1998[72] Design: R C Open Duration of follow-up: 5 years	**<u>Inclusion criteria</u>**: - already enrolled in the OSTPRE study - post-menopausal: 6-24 months since last menstruation **<u>Exclusion criteria:</u>** - contra-indications for HRT: history of breast or endometrial cancer, thromboembolic diseases, medication-resistant hypertension	N = 464 **Mean age**: 52,7 years **Gender distribution:** 100% women **Vitamin D status at baseline:** unknown **Bone status (osteoporosis, previous fractures? BMD?)** - previous fractures known, BMD measured at baseline - both subjects with and without previous fractures **Dietary calcium intake?** - Measured by questionnaire - mean: 830 mg/day **Concomitant medication?** Hormone replacement therapy for some groups (not taken into account for this study)	*(1)HRT (sequential combination of 2 mg estradiol valerate and 1 mg cyproterone acetate)* *(n= 116)* *(2) 300 IU/day vit D during 4 years and 100 IU/D during the 5th year* *plus calcium lactate 500 mg/day* *(n= 116)* *(3) HRT+Vit D* *(n=110)* *(4) Placebo* *calcium lactate 500 mg daily)* *(n=113)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING: I, open trial** • **FOLLOW-UP:** • Lost-to follow-up: 5% • Drop outs & exclusions: 20% • Described: yes • Balanced across groups: no (more drop outs in groups with HRT) • **ITT:** yes • **FUNDING**: **unknown** • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** : - open trial • **Main finding**: non-significant reduction of number of fractures and number of women with fractures • Low number of events

Pfeifer 2000[71] Design: R C DB Duration of follow-up: 1 years (treatment: 8 weeks)	**<u>Inclusion criteria:</u>** - community-living women aged 70 years or older - healthy - Serum 25(OH)D below 50 nmol/l **<u>Exclusion criteria:</u>** - hypercalcaemia - primary hyperparathyroidism - osteoporotic extremity fracture - intolerance to vitamin D or calcium - chronic renal failure - drug, alcohol, caffeine, or nicotine abuse - diabetes mellitus - treatment with bisphosphonate, calcitonin, vitamin D or metabolites, oestrogen, tamoxifen in past 6 months; fluoride in last 2 years; anticonvulsants or medications possibly interfering with postural stability or balance (e.g. anticonvulsants)	N = 148 **Mean age:** 74.8 ± 0.5 years **Gender distribution:** 100% women **Vitamin D status at baseline:** Serum 25(OH)D below 50 nmol/l measured by radio-immunoassay **Bone status (osteoporosis, previous fractures? BMD?)** previous osteoporotic fracture = exclusion primary prevention only **Dietary calcium intake?** Assessed by food frequency questionnaire, not reported **Concomitant medication?** Described: benzodiazepines, thyroidotherapy, cardiovascular drugs (1/3 on cardiovascular drugs)	*1) 1200 mg of calcium + 800 IU vit D per day (n=70)* *2) 1200 mg of Calcium / day (n=69)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate for participants, unclear for assessors • **FOLLOW-UP:** • Lost-to follow-up, drop outs & exclusions: -6% for intervention group, -9% for placebo group • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**:Strathmann AG (**industry**) provided the drugs and funding for the study • **SELECTIVE REPORTING:** no • **Other important methodological remarks** - power calculation made - primary prevention only - high compliance (mean >95% (SD 10 to 12%) • **Main finding:** significantly less falls in Ca and vit D group

Pfeifer 2009[74] Design: RCT DB MC Duration of follow-up: 20 months (treatment: 12 months)	**Inclusion criteria:** - healthy ambulatory men and women - 70 years or older - 25(OH)D <78 nmol/L **Exclusion criteria:** - hypercalcaemia, primary hyperparathyroidism, - diabetes mellitus and cardiovascular disease - fractures of the extremities due to osteoporosis - Drug exclusions: thiazides, bisphosphonates, calcitonin, vitamin D and vitamin D metabolites, oestrogen, anti-oestrogen in last 6 months; fluoride in last 2 years - intolerance to study medication - chronic renal failure (serum creatinine above 20% of the upper limit of the reference range) - drug or alcohol abuse; more than 20 cigarettes/ day;more than 7 cups of coffee/day - holidays along geographic latitude during the study;	N = 242 **Mean age**: 77 years **Gender distribution:** women 75%, men 25% **Vitamin D status at baseline:** Serum 25(OH)D <78 nmol/l measured by radio-immunoassay initial values between 54 and 55 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** no previous osteoporotic fractures primary prevention only **Dietary calcium intake?** Assessed by food frequency questionnaire mean: 618 mg/day **Concomitant medication?** unknown	*1) 1000 mg of calcium + 800 IU of vit D (n=121)* *2) 1000 mg of Calcium (n=121)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up unclear • Drop-out and Exclusions: unclear • Described: partly • Balanced across groups: ? • **ITT:** yes • **FUNDING**: Meda Pharma provided drugs and funding for the study. • **SELECTIVE REPORTING:** no • **Other important methodological remarks:** - compliance set 80% - power calculation was done for the detection of falls, not for fractures • **Main findings:** significant reduction of falls (RR = 0.73 (0.54 - 0.96)), non-significant reduction in the number of fractures

Prince 2008[75] Design: RCT DB Duration of follow-up: median: 1 year	**<u>Inclusion criteria:</u>** - community-dwelling, ambulant older women - 70 to 90 years - serum 25(OH)D concentration of less than 24 ng/ml (=60 nmol/l) - history of falling in the previous year **<u>Exclusion criteria</u>**: - hip Z score < -2.0 - medical conditions influencing bone metabolism - creatinine > twice reference range - fracture in past 6 months - Mini Mental State Examination score < 24 - marked neurological conditions likely to substantially impair balance or physical activity, e.g. stroke, Parkinson's disease - current consumption of vitamin D or bone active agents	N = 302 **Mean age:** 77 years **Gender distribution:** 100% women **Vitamin D status at baseline:** Intervention group mean: 18.1 ng/ml Placebo group mean: 17.7 ng/ml measured by radio-immunoassay **Bone status** (osteoporosis, previous fractures? BMD?) People with a fracture in the past six months excluded **Dietary calcium intake?** Assessed by food frequency questionnaire, no data reported **Concomitant medication?** Not reported	*1) 1000 IU/d ergocalciferol + 1000 mg/day calcium citrate* *(n = 151)* *2) 1000 mg / day calcium citrate* *(n = 151)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate, block randomisation • **BLINDING:** Adequate, participants and assessors • **FOLLOW-UP:** • Lost-to follow-up:, drop-out and Exclusions: 9% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding • **SELECTIVE REPORTING:** no • Important methodological remark: groups were not properly randomized height-wise and height is a predictor for falls - OR were adjusted for the differences in height between groups • **Main findings**: vitamin D reduced risk for having 1 or more falls (OR = 0.61 (0.37 - 0.99)

The RECORD trial group /Grant 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months	**Inclusion criteria:** osteoporotic fracture in the previous 10 years **Exclusion criteria:** bed or chair-bound before fracture cognitive impairment cancer in the past 10 years with risk of bone metastasis fracture associated with bone abnormality hypercalcaemia renal stone in the past 10 years life expectancy less than 6 months individuals known to be leaving the UK daily intake of more than 200 IU vit D or more than 500 mg of Ca supplements intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** measured in a subgroup by straight-phase HPLC mean: 15.2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*1) 800 IU vit D3 (n=1343)* *2) 800 IU vit D3 & 1000 mg Ca as calcium carbonte (n=1306)* *3) 1000 mg Ca as calcium carbonate (n= 1311)* *4) matching placebos (n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no

Table 41 : characteristics of included studies from meta-analysis

5.5.3 Summary and conclusions. Vitamin D plus calcium versus calcium

Vitamin D plus calcium versus calcium			
Bibliography: meta-analysis AVENELL 2014[2]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Fractures, hip *mixed primary and secondary prevention*	7411 (7)	RR = 0.84 (0.63 – 1.13) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for diversity of populations and interventions Imprecision: OK
Fractures, hip *secondary prevention*	2681 (2)	RR = 0.96 (0.65 – 1.41) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: NA, Avenell 2004 is a trial embedded in RECORD 2005 and number of patients from Avenell (130) much lower than number from RECORD (over 5000 patients) Directness: -1 Imprecision: OK
Non-vertebral fractures *mixed primary and secondary prevention*	3336 (6)	RR = 0.96 (0.79 – 1.16) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1, for diversity of populations and interventions Imprecision: OK
Non-vertebral fractures *secondary prevention*	2681 (2)	RR = 1.00 (0.82 – 1.22) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: NA Directness: OK Imprecision: OK
Vertebral fractures *Secondary prevention only*	2681 (2)	RR = 0.14 (0.01 – 2.77) *NS*	⊕⊕⊖⊖ **LOW** Study quality: OK Consistency: NA, Avenell 2004 is a trial embedded in RECORD 2005 and number of patients from Avenell (130) much lower than number from RECORD (over 5000 patients) Directness: OK Imprecision: -1, large CI
Fractures, all *mixed primary and secondary prevention*	8812 (11)	RR = 0.87 (0.74 – 1.02) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for diverse population and interventions Imprecision:OK

Fractures, all *secondary prevention*	2681 (2)	RR = 0.98 (0.80 – 1.20) *NS*	⊕⊕⊕⊖ **MODERATE** Study quality: OK Consistency: OK Directness: -1 for differences in populations and interventions Imprecision: OK

Table 42: summary and conclusion vitamin D plus calcium versus calcium

The 2014 Cochrane meta-analysis by Avenell provides data on 11 trials investigating the effect of vitamin D and calcium on fractures, compared with calcium.

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of hip fractures compared with calcium in people both with and without a previous fracture.
Grade: MODERATE level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of hip fractures compared with calcium in people having already suffered a previous fracture
Grade: LOW level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of non-vertebral fractures compared with calcium in people both with and without a previous fracture.
Grade: MODERATE level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of non-vertebral fractures compared with calcium in people having already suffered a previous fracture
Grade: LOW level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of vertebral fractures, compared with calcium, in people having already suffered a previous fracture
Grade: LOW level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of any fracture, compared with calcium in people both with and without a previous fracture.
Grade: MODERATE level of evidence

Treatment with vitamin D and calcium combined, does not significantly reduce the risk of any fracture, compared with calcium, in people having already suffered a previous fracture
Grade: MODERATE level of evidence

6. RESULTS: CALCIUM AND VITAMIN D FOR PREVENTION OF FALLS

6.1 Introduction

A literature search was carried out as previously described. Comparing references to clinical trials with reviews and meta-analyses lead to selection of two Cochrane reviews as source documents on calcium and vitamin D for prevention of falls. Gillespie et al. (2012)[3] deal with prevention of falls in community dwelling patients, whereas Cameron et al. (2012)[4] deal with fall prevention in institutionalised patients. Neither more recent references, nor other complementary references were selected for inclusion in this analysis.
Two additional meta-analyses and a critical review were used in the discussion and the critical reflections at the end of this chapter.

Before dealing with the tables reviewing the clinical evidence profile, the characteristics of the individual studies taken from the meta-analyses and the summary and conclusions, an overview is given with the search strategy and the inclusion criteria for the recruited patients. This overview is followed by the conclusion of the authors.

Gillespie et al. (2012)[3] prevention of falling in community dwelling patients. Search strategy and inclusion criteria

Reference: Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for preventing falls in older people living in the community (Review). The Cochrane Library 2012, Issue 9.

Search strategy
The authors searched the Cochrane Bone, Joint and Muscle Trauma Group Specialized Register (February 2012), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2012, Issue 3), MEDLINE (1946 to March 2012), EMBASE (1947 to March 2012), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to February 2012), and online trial registers. They did not apply any language restrictions. In MEDLINE (OvidSP) subject-specific search terms were combined with the sensitivity-maximising version of the MEDLINE trial search strategy (Lefebvre 2011), but without the drug therapy floating subheading which produced too many spurious references for this review. The strategy was modified for use in *The Cochrane Library,* EMBASE, and CINAHL.

Inclusion criteria
Overall, 70% of included participants were women. In some studies all participants were women (Sanders et al. 2010[57]; Kärkäinen et al. 2010[76]; Porthouse et al. 2005[65]).
The inclusion/exclusion criteria and other participant details are listed for each study in the characteristics of included studies.
Lower serum vitamin (i.e. vitamin D insufficiency or deficiency) was an inclusion criterion in two trials of vitamin D supplementation (Pfeifer 2000[71]; Pfeifer 2009[74]).

Gillespie et al. (2012): conclusion by the authors

Reference: Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, Lamb SE. Interventions for preventing falls in older people living in the community (Review). The Cochrane Library 2012, Issue 9.

Vitamin D supplementation with or without Calcium in community dwelling patients:

Overall, vitamin D did not reduce either rate of falls or risk of falling, whether or not the trial had recruited only people at higher risk of falling. However, subgroup analysis showed that supplementation appeared effective in reducing rate of falls and risk of falling when administered to those selected on the basis of lower vitamin D levels at enrolment.

Cameron et al. (2012)[4]: prevention of falling in institutionalized patients. Search strategy and inclusion criteria.

Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in care facilities and hospitals (Review); The Cochrane Library 2012; Issue 12

Search strategy

The authors searched the Cochrane Bone, Joint and Muscle Trauma Group Specialized Register (March 2012), the Cochrane Central Register of Controlled Trials (The Cochrane Library 2012, Issue 3), MEDLINE (1946 to March 2012), EMBASE (1980 to March 2012), and CINAHL (1982 to March 2012). They searched ongoing trial registers via the World Health Organisation's ICTRP Search Portal (August 2012). No language restrictions were applied. In MEDLINE (OvidSP) subject-specific search terms were combined with the sensitivity- and precision-maximising version of the MEDLINE trial search strategy (Lefebvre 2011). We modified this strategy for use in The Cochrane Library, EMBASE, and CINAHL.

They also checked reference lists of articles and further trials were identified by contact with researchers in the field. For the first version of this review, we identified trials in care facilities and hospitals included in Gillespie 2003.

Inclusion criteria

Trials of interventions to prevent falls in older people, of either sex, in care facilities or hospitals were included. Trials were considered for inclusion if the majority of participants were over 65 years or the mean age was over 65 years, and the majority were living in residential or nursing care facilities or were patients in hospital. Trials with participants resident in the community and in care facilities were either included in this review or the Cochrane review of interventions for preventing falls in older people living in the community (Gillespie 2012)[3], depending on the proportion of participants in each setting. They would have been included in both reviews if data were provided for subgroups based on setting. Inclusion in either review was determined by discussion between the authors of both reviews.

Cameron et al. 2012: conclusion by the authors.

Cameron ID, Gillespie LD, Robertson MC, Murray GR, Hill KD, Cumming RG, Kerse N. Interventions for preventing falls in older people in care facilities and hospitals (Review); The Cochrane Library 2012; Issue 12

Vitamin D supplementation with or without Calcium in institutionalized patients: conclusion by the authors

Three trials tested the effect of vitamin D3 supplementation on falls (Bischoff 2003[67]; Chapuy 2002[62]; Flicker 2005[73]). Overall, pooled data showed a statistically significant reduction in rate of falls. Pooled data did not show a reduction in the risk of falling. Average serum vitamin D levels at baseline appeared to be low or very low in all studies (see Characteristics of included studies), therefore these results are only applicable to residents with low vitamin D levels.

6.2. Vitamin D3 versus placebo

Data is extracted from the Cochrane reports by Gillespie et al (2012)[3] and Cameron et al(2012)[4] (see section 6).
An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies were found.

6.2.1 Vitamin D versus placebo in community-dwelling patients

The Cochrane report by Gillespie et al (2012)[3] did not report on any studies comparing vitamin D3 (cholecalciferol) and placebo in community-dwelling patients with a habitual schedule (a number of studies with a different dosing schedules are reported in section 6.5).
For the sake of completion, the research group compared studies included in another meta-analysis (Murad 2011[87]) but found only one supplemental prospective study by Graafmans et al. 1996[77]. This study examines the relations between falls and risk factors, and subjects were members of a cohort that had participated in a clinical trial by Lips et al. 1996[78]. Due to the uncertainty about how the OR was calculated, and the numbers on which the calculation is based, this study is not analysed in this report.

6.2.2. Vitamin D versus placebo in institutionalized patients

Cameron et al. (2012)[4] incorporated two studies done with ergocalciferol. These studies are not evaluated in detail, because in Belgium there are no medicines registered with ergocalciferol as mono preparations or in combination with calcium.

One study (Broe et al. 2007)[79] enrolled 48 patients (mainly women), and in the other study 3717 patients were enrolled (Law et al. 2006)[50]. Three quarter of the patients were women. They received ergocalciferol daily (increased dosing over 5 months periods; only one dose of 800 IU evaluated) or a shot every 3 months. Both studies gave positive outcomes for the rate of falls, but not for the number of fallers. When the rate of falls of both studies were combined, the global rate of falls was no longer significantly different from placebo, probably because Law et al. (2006)[50], found a relative risk of rate of falls close to 1 and the rate of falls found by Broe et al. (2007)[79] showed an important spread.
The results of both studies are pooled with other results in section 6.6.

6.3. Vitamin D3 plus Calcium versus placebo

Data is extracted from the Cochrane reports by Gillespie et al (2012)[3] and Cameron et al(2012)[4]. (see section 6)
An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies were found, however we found the proceedings of a new trial of vitamin D and calcium versus placebo that is being conducted and that might deliver results in the future (Lopez-Torres et al. 2011[80])

6.3.1 Vitamin D3 plus calcium versus placebo in community-dwelling patients

6.3.1.1. Rate of falls and number of fallers in community dwelling patients

Ref	**Comparison:**	**Results**		
Gillespie 2012	**Vit D+ Ca vs placebo**	**intervention** Mean (SD) or event rate	**control** Mean (SD) or event rate	**RR (95% CI)**
Rate of Falls				
Bischoff-Ferrari 2006[81], Kärkäinen 2010[76], Porthouse 2005[65]		N = 3 (number of studies) n = 435 + 3139 + 3002 = 6586 (= number of patients taken from the forest plot)		Bischoff-Ferrari (2006) Effect of VitD3 + Ca : RR = 0.77 (0.51-1.15) not significant *Note:* *Women (n=399) : RR = 0.54 (0.30-0.97) significant* *Less active women (n=221) : RR = 0.35 (0.15-0.81) significant* Kärkäinen (2010) Effect of VitD3 + Ca : RR = 1.05 (0.91-1.20) not significant Porthouse (2005) Effect of VitD3 + Ca : RR = 0.98 (0.79-1.20) not significant
		Bischoff-Ferrari 2006 Not communicated Kärkäinen 2010 Not communicated Porthouse 2005 Not communicated n = 2910 Number taken from forest plot	Bischoff-Ferrari 2006 Not communicated Kärkäinen 2010 Not communicated Porthouse 2005 Not communicated n = 3666 Number taken from forest plot	
Number of fallers				
Bischoff-Ferrari 2006[81], Kärkäinen 2010[76], Porthouse 2005[65]		N = 2 (number of studies) n = 435 + 3139 + 3002 = 6586 (= number of patients taken from the forest plot)		Bischoff-Ferrari (2006) RR = 0.77 (051-1.16) not significant Kärkäinen (2010) RR = 0.98 (0.92-1.04) not significant Porthouse (2005) RR = 0.98 (0.79-1.22) not significant
		Bischoff-Ferrari 2006 107 on 219 pts. (48.9%) Kärkäinen 2010 812 on 1566 pts. (52%) Porthouse 2005 Not communicated	Bischoff-Ferrari 2006 124 on 216 pts. (54.9%) Kärkäinen 2010 833 on 1573 pts. (53%) Porthouse 2005 Not communicated	

Table 43: clinical evidence profile vitamin D plus calcium versus placebo

6.3.1.2 Characteristics of studies with as outcomes rate of falls and number of fallers in community dwelling patients

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Bisschoff-Ferari 2006[81] Design: RCT DB PL Follow-up: 3 year	Inclusion – men and women ≥ 65 years; – living in the community. – written informed consent; Exclusion • bisphosphonate, calcitonin, estrogen, tamoxifen citrate, or testosterone in the past 6 months or fluoride in the past 2 years; • renal disease or renal stone in the past 5 years; • current cancer, hyperparathyroidsm, dietary calcium intake exceeding 1500 mg/d, or laboratory evidence of kidney- (serum creatinine level >1.2 mg/dL [> 106.1 µmol/L]) or liver disease	• N = 445: Pl (226) – V (219) * Mean age: 70-71 y * Gender distribution: women N=245; men N=199 * VitD status at baseline: between 25 and 33 ng/ml (deficient = below 32 ng/ml) * Bone status: no data * Dietary Ca intake: between 667 and 790 mg/d * Concomitant medication: no data * Activity index scored	Randomization stratified (sex; race; decade of age Placebo Verum: vitD3: 700 IU/d + Ca-citrate 500 mg/d	• **ALLOCATION CONCEALMENT**: adequate • **RANDOMISATION:** not clear • **BLINDING:** double blind: adequate • **FOLLOW-UP:** • Drop-out and Exclusions: 17 % (V) / 13 % (Pl) • **ITT:** yes (+ PP analysis) • **FUNDING**: no company funding • **SELECTIVE REPORTING:** no, but analysis on predefined subgroups, mainly women and men • **Other important methodological remarks**: • - no reporting on power calculation; • - no reporting on compliance • **Main outcome**: fall reduction in women (46%), especially in less active women (- 65%). No significant fall reduction in men

Kärkäinen 2010 Design R Open Follow-up 3 year	Inclusion • Women • 65 years • Not belonging to a former osteoporosis study sample Exclusion • Belonging to the OSTRE bone densitometry sample	• N = 3432: • C (1714) – Intervention (1718) • Subgroups of 375 patients in both arms • • Mean age: 67 years • Gender: only women • Vitamin D status at baseline: 51.3 (19.8) nmol/l (not falling) and 48.7 (17.4) nmol/l (experiencing a fall) (< 80 nmol/l = considered deficient) • Bone status: no BMD measured • Dietary Ca intake: mean 892 mg/d • Concomitant medication: HT 56.5% (no intervention) / 52.9% (intervention); 2.5 to 2.8 prescribed medicines per person	Randomization by an independent statistician: two groups equal size without blocking or stratification or random allocation sequence No intervention: continue dietary habits Intervention: + 800 IU VitD + 1000 mg Ca-carbonate • Randomized subsample for VitD measurement	• **ALLOCATION CONCEALMENT**: at random • **RANDOMISATION:** no detailed description • **BLINDING:** open study • **FOLLOW-UP:** • Lost-to follow-up: 17 (intervention) and 29 patients (control) • Drop-out and Exclusions: 180 patients in intervention group discontinued treatment (included in final analysis) • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • - Open label study • - No power calculation • - Relatively high total Ca intake in intervention group
Porthouse 2005 Open R C Median follow-up of 25 months	Inclusion — ≥ 70 years — ≥ 1 risk factor for hip fracture Exclusion • Ca-supplementation of > 500 mg/d • Kidney or bladder stones; renal failure; hypercalcemia	• N = 3314 (control = 1993; intervention = 1321) • Age: mean 77 ± 5 years • Gender: only women • VitD status: not checked • Bone status: not measured • Dietary Ca-intake: not reported • Co-medication: not reported	Control Supplement use in control group after 18 months: 5.7% (amount of Ca and VitD not mentioned) Intervention • Ca-carbonate 1000 mg/d • VitD 800 IU/d • Dose divided over 2 intakes/d	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear, states “randomized” (control vs intervention randomized to 3:2) • **BLINDING:** open design • **FOLLOW-UP:** • Lost-to follow-up: control group (1.6 %) intervention (33%) • Described: no • Balanced across groups: no • **ITT:** yes • **FUNDING**: only study medication provided by company • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • - Pilot study undertaken; patients of pilot study included for analysis (N = 117) • - Adherence in intervention group relatively low: after 18 months = 58.6%

Table 44: characteristics of included studies from evidence profile in above-mentioned meta-analyses

6.3.1.3. Summary and conclusions for vitamin D plus calcium versus placebo in community-dwelling patients

Vitamin D3 and Ca versus placebo			
Bibliography: meta-analysis GILLESPIE et al. 2012[3]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	6586 (3) Follow-up of 2 to 3 years	RR = **0.96 (0.89-1.04)** NS	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Two of three studies R, one DB and C, one open design: +3 Randomization unclear in two of three studies: -1 Consistency: all studies gave the same outcomes: no change in rating Directness: doses of VitD3 comparable, dose of Ca different: -1 Imprecision: no change in rating
Number of fallers	6586 (3) Follow-up of 2 to 3 years	RR = **0.98 (0.92-1.03)** **NS**	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Two of three studies R, one DB and C, one open design:: +3 Randomization unclear in two of three studies: -1 Consistency: all studies gave the same outcomes: no change in rating Directness: doses of VitD3 comparable, dose of Ca different: -1 Imprecision: no change in rating

Table 45: summary and conclusions for vitamin d plus calcium versus placebo in community-dwelling patients

Comments

Patients included in the studies had a mean age of 65+ and were predominantly women. They were not consistently characterized over the studies with regard to vitamin D status, physical activity, bone mineral density, dietary calcium intake and concomitant medicines. When vitamin D status was reported, most of the patients were deficient.
The number of patients in the original studies does not correspond to the number taken into account for the meta-analysis: e.g. Kärkäinen et al. (2010)[76]: the number mentioned in the abstract fits with the forest plot in the meta-analysis, but in the flow chart only 2546 patients were taken into the ITT-analysis; e.g. Porthouse et al. (2005)[65]: 3002 patients in the meta-analysis vs. 3314 included according to the original publication.

The dose of vitamin D and calcium was given daily and varied between 700 and 800 IU per day. Calcium was mostly administered as Ca-carbonate in a dose of 1000 mg Ca-carbonate per day. This dose contains 400 mg elementary calcium. Bischoff-Ferrari et al. (2006)[81] used Ca-citrate in a daily dose of 500 mg, which contains only 120 mg of elementary calcium. With this low dose,

dietary calcium intake becomes important. It was estimated between 667 and 790 mg/d. As calcium intake with food as primary source is more important than the supplement, the difference between placebo group and the intervention group becomes modest.
The number of fallers was not reported by Porthouse et al. (2005)[65]. For this study results were directly taken from the forest plot.
The combination of vitamin D with different doses of calcium did not lead to a significant lowering of falls and of fallers. Nevertheless, in the subgroup of women, Bischoff-Ferrari et al. (2006)[81]significantly lowered the rate of falls, an effect which was even stronger in the less-exercised subgroup. However this cannot be taken into account as this study is not powered for subgroup analysis.
When reported, adherence was not optimal as it was situated around 60%.

Conclusion

Treatment with vitamin D plus calcium versus placebo does not significantly reduce the risk of falling for people living in the community.
GRADE : VERY LOW level of evidence

Treatment with vitamin D plus calcium versus placebo does not significantly reduce the number of fallers for people living in the community.
GRADE : VERY LOW level of evidence

6.3.2. Vitamin D3 plus calcium versus placebo in institutionalized patients

6.3.2.1. Rate of falls and number of fallers in institutionalized patients

Ref	**Comparison:**	**Results**		
Cameron 2012[4]	**Vit D3 + Ca vs placebo**	**intervention** Mean (SD) or event rate	**control** Mean (SD) or event rate	**RR (95% CI)**
Rate of falls: no studies				
Number of fallers				
Chapuy 2002[62]		N = 1 (number of studies) n = 583 (number of patients)		RR = 1.03 (0.90-1.18) not significant
		Not mentioned	Not mentioned	

Table 46: clinical evidence profile for vitamin D + calcium versus placebo in institutionalized patients

6.3.2.2. Characteristics of studies with as outcomes rate of falls and number of fallers in institutionalized patients

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Chapuy 2002[62] MC / R / DB / PL Follow-up: 2 years	<u>Inclusion</u> Living in apartment houses for elderly Ambulatory: able to walk with cane of walker Life expectancy of ≥ 24 months <u>Exclusion</u> Intestinal malabsorption Hypercalcemia Chronic renal failure Taking drugs to alter bone metabolism: corticosteroids; anticonvulsants; thyroxine (high doses); F-salts, bisphosphonates, calcitonin, Ca (> 500 mg/d) and VitD3 (> 100 IU/d)	N = 583 Mean age: 85-86 y Gender distribution: only women Vitamin D status at baseline: 9.16 to 9.24 ng/ml BMD measured: femoral, neck, forearm Ca-intake: 550-565 mg/d Concomitant medication: see exclusion criteria	<u>Group 1</u> Ca-VitD3 fixed combination Ca = 1200 mg elementary Ca Vit D3 = 800 IU <u>Group 2</u> Ca-VitD3 separately Ca = 1200 mg elementary Ca VitD3 = 2 tablets of 400 IU <u>Group 3</u> Placebo	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** unclear • **BLINDING:** participants and assessors: adequate • **FOLLOW-UP:** • drop-out rates similar in the three groups (27.2% in the Ca–D3 group, 29.1% in Ca+D3 group and 36.1% in the placebo group). • Described: yes • Balanced across groups: yes/no • **ITT:** yes • **FUNDING**: sponsoring by Merck, Darmstadt • **SELECTIVE REPORTING:** no • **Other important methodological remarks** Compliance > 95% • Primary and secondary outcomes? • Not powered for hip fracture risk •

Table 47: characteristics of included studies in the above-mentioned meta-analysis from evidence profile

6.3.2.3. Summary and conclusions for vitamin D3 plus calcium versus placebo in institutionalized patients

Vitamin D3 and Ca versus placebo			
Bibliography: meta-analysis CAMERON et al. 2012[4]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	No studies		
Number of fallers	583 (1) Follow-up of 2 years	RR = 1.03 (0.90-1.18) NS	⊕⊕⊖⊖ **LOW EVIDENCE** RCT: + 4 Allocation concealment and randomization unclear: -1 Consistency: NA, only one study: -1 Directness: not applicable Imprecision: no change in rating

Table 48: summary for vitamin D plus calcium for institutionalized patients

Comments

As the mean age of the population studied is above 80, this population is at relatively high risk of falling. The study included only women with a deficient vitamin D status. BMD was measured. Supplemented plus dietary calcium intake are expressed as elementary calcium and amounted above 1700 mg, which can be considered as high. The patients were screened on concomitant medication.

Conclusion

Treatment with calcium and vitamin D did not significantly lower the number of fallers in people living in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade : LOW level of evidence

6.4. Vitamin D3 plus Calcium versus Calcium

Data is extracted from the Cochrane reports by Gillespie et al (2012)[3] and Cameron et al(2012)[4] (see section 6).
An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies were found.

6.4.1. Vitamin D3 plus calcium versus calcium in community-dwelling patients

6.4.1.1. Rate of falls and number of fallers in community dwelling patients

Ref	**Comparison :**	**Results**		
Gillespie 2012[3]	**Vit D3 + Ca vs Ca**	**intervention** Mean (SD) or event rate	**control** Mean (SD) or event rate	**RR (95% CI)**
Rate of falls				
Pfeifer 2000[71]		N = 1 (number of studies) n = 137 (number of patients)		VitD3 + Ca vs. Ca : RR = 0.54 (0.30-0.98) SS
		17 falls on 70 pts. (24%)	30 falls on 67 pts. (45%)	
Number of fallers				
Pfeifer 2000[71], Pfeifer 2009[74]		N = 2 (number of studies) n = 379 (number of patients)		
		Pfeifer 2000 11 on 70 pts. (16%)	Pfeifer 2000 19 in 67 pts. (28%)	Pfeifer 2000 VitD3 + Ca vs. Ca : RR = 0.55 (0.28-1.07) not significant
		Pfeifer 2009 40% n = 122	Pfeifer 2009 63% n = 120	Pfeifer 2009 VitD3 + Ca vs. Ca : RR = 0.73 (0.55-0.98) significant

Table 49: clinical evidence profile vitamin D plus calcium versus calcium, community-dwelling patients

6.4.1.2. Characteristics of studies with as outcomes rate of falls and number of fallers in community dwelling patients

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Pfeifer 2000 DB C Follow-up 1 year	Inclusion • ≥ 70 years • Healthy women • VitD (25 OH VitD) < 50 nmol/l Exclusion • hypercalcaemia • Primary hyperparathyroidemia • Fractures caused by osteoporosis • Therapy with bisphosphonates, calcitonin, vitD or VitD metabolites, estrogen, tamomxifen in the past 6 months • Chronic renal failure • Nicotine or alcohol abuse • More than 7 cups of coffee/d • Diabetes mellitus • Medication interfereing with postural stability and balance (e.g. anticonvulsants)	• N = 148 (equally distributed over 2 arms) • Age: mean 74.8 ± 0.5 years • Gender: only women • VitD status: < 50 nmol/l: initial values between 25-26 nmol/l (25-OH VitD) and between 36-38 nmol/l (1,25-OD VitD); serum PTH; serum osteocalcin; serum alkaline phosphatase; urinary creatinine ratio's • Other parameters measured: serum ionized Ca; • Bone status: not measured • Dietary Ca-intake: assessed semiquantitatively but not reported • Co-medication: see exclusion criteria; 1/3 on cardiovascular drugs	Two arms: during 8 weeks • Ca-carbonate 600 mg/d or • Ca-carbonate 600 mg/d + VitD 400 IU • 2x daily • No supplements by patients on their own allowed • After 8 weeks therapy was discontinued (no further details) Evaluation After 8 weeks • After 1 year	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate for participants, unclear for assessors • **FOLLOW-UP:** • Response rates after 1 year: 91% (Ca) and 95% (Ca + VitD) • Described: yes • Balanced across groups: yes • **ITT:** not specified • **FUNDING**: company funding (Strathman AG Hamburg) • **SELECTIVE REPORTING:** no • **Other important methodological remarks** - Extensive list of exclusion criteria - Power calculation made - Restrictions on co-medication mentioned - Fractures by osteoporosis excluded - VitD metabolites specifically measured - Compliance measured: mean ≥ 95% (SD 10 to 12%) - what happened after 8 weeks as supplementation is concerned?

Pfeifer 2009 DB C MC Follow-up 20 months	Inclusion • ≥ 70 years • Healthy subjects • VitD (25 OH VitD) < 78 nmol Exclusion • Hypercalcemia • Primary hyperparathyroidemia • Fractures caused by osteoporosis • Therapy with thiazide, bisphosphonates, calcitonin, vitD or VitD metabolites, estrogen, tamoxifen in the past 6 months • Chronic renal failure • Nicotine or alcohol abuse • More than 7 cups of coffee/d • Diabetes mellitus • Medication interfering with postural stability and balance (e.g. anticonvulsants)	• N = 242 (equally distributed over 2 arms) • Age: mean 76 and 77 ± 4 years • Gender: 25 and 26% men • VitD status: initial values between 54 and 55 nmol/l (25-OH VitD) • Other parameters measured: serum ionized Ca • Bone status: not measured • Dietary Ca-intake: assessed semiquantitatively but not reported • Co-medication: see exclusion criteria, but no medication history mentioned	Two arms: during 12 months • Ca-carbonate 500 mg • Ca-carbonate 500 mg + VitD 400 IU • 2x daily • Thereafter 8 months follow-up without treatment Evaluation After 12 months After 20 months	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Excluded for the PP-analysis: 31 subjects (mainly by non-compliance) • Described: partly • Balanced across groups: not specified • **ITT:** yes • **FUNDING**: study medication and study sponsorship by Meda Pharma • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • - Compliance set 80 % • - Extensive exclusion criteria • - Power calculation made based upon the number of falls (not on the number of fractures)

Table 50: characteristics of included studies in above-mentioned meta-analysis from evidence profile

6.4.1.3. Summary and conclusions for vitamin D3 plus calcium versus calcium in community-dwelling patients

Vitamin D3 and Ca versus calcium			
Bibliography: meta-analysis GILLESPIE et al. 2012[3]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	137 (1) Follow-up 1 year	RR = 0.54 (0.30-0.98) ***SS***	⊕⊕⊖⊖ **LOW EVIDENCE** Two RCT's: +4 Randomization unclear in one of two studies: -1 Consistency: outcomes are converging, although combination of two studies is necessary for number of fallers: no change in rating Directness: treatment regimen comparable: no change in rating Imprecision: relatively low number of patients: -1
Number of fallers	379 (2) Follow-up 1 year to 20 months	RR = **0.70 (0.53-0.92)** **SS**	⊕⊕⊖⊖ **LOW EVIDENCE** Two RCT's: +4 Randomization unclear in one of two studies: -1 Consistency: outcomes are converging, although combination of two studies is necessary for number of fallers: no change in rating Directness: treatment regimen comparable: no change in rating Imprecision: relatively low number of patients: -1

Table 51: summary vitamin D plus calcium versus calcium in community-dwelling patients

Comments

The included patients were mainly women, aged 70+. They had deficient vitamin D levels. There were extensive exclusion criteria. The number of patients enrolled in the study does not always correspond with the number mentioned in the forest plot from the Cochrane meta-analysis of Gillespie et al. 2012[3] (like for Pfeifer et al. 2000[71]).
The combination VitD3 + Ca significantly lowered the rate of falls when compared with Ca alone. Where the number of fallers is concerned, both studies separately showed inconsistent effects. When taken together, the number of fallers was significantly lower in the combination group as compared to the monotherapy with calcium. In both studies compliance was measured and evaluated as being at least 80%.

Conclusion

Treatment with vitamin D plus calcium compared with calcium significantly reduces the rate of falling in people living in the community.
Grade : LOW level of evidence

Treatment with vitamin D and calcium compared to calcium significantly reduces the number of fallers in people living in the community.
Grade : LOW level of evidence.

6.4.2. Vitamin D3 plus calcium versus calcium in institutionalized patients

6.4.2.1. Rate of falls and number of fallers in institutionalized patients

Ref	**Comparison:**	**Results**		
Cameron 2012[4]	**Vit D3 + Ca vs Ca**	**intervention** Mean (SD) or event rate	**control** Mean (SD) or event rate	**RR (95% CI)**
Rate of falls				
Bischoff 2003[67], Flicker 2005[73]		N = 2 (number of studies) n = 747 (number of patients)		Bischoff (2003) Reduction in falls by VitD3 + Ca vs. Ca : 62% (37-77%) significant (P <0.0002) RR = 0.51 (0.23-1.14) not significant Flicker (2005) Effect of VitD3 + Ca vs. Ca alone : RR = 0.73 (0.57-0.95) significant
		Not communicated (total n = 375)	Not communicated (total n = 372)	
Number of fallers				
Bischoff 2003[67], Flicker 2005[73]		N = 2 (number of studies) n = 747 (number of patients)		Bischoff (2003) RR = 0.70 (0.31-1.56) not significant Flicker (2005) RR = 0.86 (0.69-1.07) not significant
		Bischoff 2003 14 on 62 patients = 22.6% Flicker 2005 54% Total n = 375	Bischoff 2003 18 on 60 = 30.0% Flicker 2005 59% Total n = 372	

Table 52: clinical evidence profile vitamin D + calcium versus calcium in institutionalized patients

6.4.2.2. Characteristics of studies with as outcomes rate of falls and number of fallers in institutionalized patients

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Bischoff 2003[67] DB / R / C Follow-up: 12 weeks Study done during winter months	<u>Inclusion</u> Elderly in long-stay geriatric care <u>≥</u> 60 years Able to walk 3 m with or without walking aid Previous VitD supplementation allowed <u>Exclusion</u> Hyperparathyroidism Hypocalcemia Hypercalcuria Renal insufficiency Fracture or stroke during last 3 months HRT, calcitonin, F-salts, bisphosphonates during the previous 24 months	N = 122 Mean age: 85 Gender distribution: only women Vitamin D status at baseline: not measured (19% received VitD treatment before) Bone status: no data Dietary Ca intake: 600-700 mg/d Concomitant medication: see exclusion criteria	<u>Group 1</u> 600 mg Ca-carbonate + VitD 400 IU 2x/d <u>Group 2</u> 600 mg Ca-carbonate 2x/d •	• **ALLOCATION CONCEALMENT**: unclear • **RANDOMISATION:** unclear • **BLINDING:** Participants, personnel and assessors: adequate. • **FOLLOW-UP:** • Drop-out and Exclusions: <u>+</u> 25 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: Stratham AG • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • Power calculation based on 30% drop-out

Flicker 2005[73] R / PL / C / DB Follow-up: 2 years	<u>Inclusion</u> Institutionalised elderly No further restrictions mentioned <u>Exclusion</u> Medication affecting bone and mineral metabolism: e.g. warfarin, chronic heparin therapy, Vit D therapy within the past 3 months, glucocorticoids (> 5 mg prednisolone during ≥ 1 month), bisphosphonates, HRT Thyrotoxicosis within past 3 years Primary hyperparathy-roidism in the past 3 years Multiple myeloma Paget's disease of bone History of malabsorption Intercurrent active malignancy Disorders affecting bone and mineral metabolism	N = 625 Mean age: 83-84 y Gender distribution: 95% women Vitamin D status at baseline: 25-90 nmol/l (only 11% between 61-90 nmol/l) Bone status: fractures 54% (PL) and 60% (intervention) with significantly more hip fractures in intervention group Calcium intake: no monitoring Concomitant medication: recorded but not reported	<u>Control group</u> 600 mg elementary Ca as Ca-carbonate per day <u>Intervention group</u> 600 mg elementary Ca as Ca-carbonate + 1000 IU ergocalciferol per day *Note: initially patients were given 10,000 IE ergocalciferol per week. This dose changed to 1000 IU ergocalciferol per day, when the production of the 10,000 IU tablets was discontinued.*	• **ALLOCATION CONCEALMENT**: adequate • **RANDOMISATION:** patients with low ergocalciferol not randomized • **BLINDING:** Participants, personnel as well as assessors: acceptable but not adequate • **FOLLOW-UP:** • Drop-out: after 1 year 22% (PL) and 24% (intervention); after 2 years 42% (PL) and 41% (intervention) • Described: yes • Balanced across groups: yes • **ITT:** no, withdrawals and deaths excluded from analysis • **FUNDING**: institutional • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • ≥ 50% compliance by 86% (PL) and 87% (intervention) • Power calculation without taking into account drop-outs

Table 53: characteristics of included studies in above-mentioned meta-analysis, from evidence profile

6.4.2.3. Summary and conclusions for vitamin D3 plus calcium versus calcium in institutionalized patients

Vitamin D3 and Ca versus calcium			
Bibliography: meta-analysis CAMERON et al. 2012[4]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	n = 747 (2) Follow-up 12 weeks to 2 years	RR = **0.71 (0.56-0.90)** ***Statistically significant***	⊕⊕⊖⊖ **LOW EVIDENCE** Two RCT's: +4 Randomization not always clear: -1 Consistency: cholecalciferol and ergocalciferol studies combined; different results with regard of the rate of falls, by combining results if two studies positive outcome in favour of the combination VitD3 + Ca: -1 Directness: treatment regimen comparable: no change in rating Imprecision: no change in the rating
Number of fallers	n = 747 (2) Follow-up 12 weeks to 2 years	RR = **0.85 (0.69-1.05)** ***NS***	⊕⊕⊖⊖ **LOW EVIDENCE** Two RCT's: +4 Randomization not always clear: -1 Consistency: cholecalciferol and ergocalciferol studies combined; different results with regard of the rate of falls, by combining results if two studies positive outcome in favour of the combination VitD3 + Ca: -1 Directness: treatment regimen comparable: no change in rating Imprecision: no change in the rating

Table 54: summary vitamin D plus calcium versus calcium in institutionalized patients

Comments

Patients had a mean age of 80+ and predominantly women. When vitamin D status was measured, approximately 90% of the patients were deficient. Dietary calcium intake was reported in one study as being 600-700 mg per day (Bischoff et al. 2003[67]). In another study the number of patients with previous falls was significantly higher in the intervention group (Flicker et al. 2005[73]).
Although in the study by Flicker et al. (2005) patients received ergocalciferol, study results were co-evaluated with Bischoff et al. (2003)[67] as being done with cholecalciferol (VitD3) in the forest plot.
Although the number of falls is significantly reduced in one study, the RR of falling is not significant in this same study, because of the considerable spreading (Bischoff et al. 2003[67]).
When this study is combined with Flicker et al. 2005[73] (done with ergocalciferol !!) , the rate of

falls is significantly lower for the combination vitamin D + calcium. There is no reduction in the number of fallers. When a subgroup analysis is done in patients with > 50% compliance the RR as well as the number of fallers is significantly reduced: RR = 0.63 (0.48-0.82). There is also a significant reduction in number of patients falling: RR = 0.70 (0.50-0.99) (Flicker et al. 2005[73]).

Conclusion

Treatment with vitamin D plus calcium compared with calcium significantly reduces the rate of falls in people living in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade : LOW level of evidence

Treatment with vitamin D plus calcium compared with calcium does not significantly reduce the number of fallers in people living in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade : LOW level of evidence

6.5. Different Vitamin D regimens

Several studies could be identified in the meta-analysis by Gillespie et al. (2012) that compared different regimens of vitamin D. One study looks at the difference between two dosages (Bischoff et al 2010)[83,] or others were RCT with dosing regimens that are unconventional for Belgium. In Belgium supplementation of vitamin D is more often scheduled daily, weekly or monthly. Two of the studies work with a single dose per year (Latham 2003[82] and Sanders 2010[57]) one with a 4-monthly schedule (Trivedi 2003[56]).

An additional search for new trials published after the search date of the selected meta-analysis was conducted. No new studies reporting falls were found.

6.5.1. Non-habitual schedules of vitamin D3 versus placebo in community-dwelling patients

6.5.1.1 Vitamin D3 versus placebo : clinical evidence profile in community dwelling patients

Ref	**Comparison:**	**Results**		
Gillespie 2012[3]	**Vit D3 vs placebo**	**intervention** Mean (SD) or event rate	**control** Mean (SD) or event rate	**RR (95% CI)**
Rate of Falls				
Latham 2003[82], Sanders 2010[57]		N = 2 (number of studies) n = 222 + 2256 = 2501 (= number of patients taken from the forest plot)		
		Latham 2003 157 falls by 108 pts. Sanders 2010 2892 falls by 1131 pts. Total 3049 –falls by 1239 pts. Total number of pts. taken from forest plot	Latham 2003 156 by 114 patients Sanders 2010 2512 by 1125 pts. Total 2668 falls by 1239 pts. Total number of pts. Taken from forest plot	Latham (2003) Relative risk of a fall : RR = 1.12 (0.79-1.59) not significant Sanders (2010) Relative risk of a fall : RR = 1.15 (1.03-1.31) significant Relative risk of a fall : RR = 1.16 (1.03-1.31): adjusted for Ca intake: significant
Number of fallers				
Latham 2003[82], Sanders 2010[57], Trivedi 2003[56]		N = 3 (number of studies) n = 222 + 2256 + 2038 = 4416 (= number of patients)		

	Latham 2003 64 on 108 pts. Sanders 2010 837 on 1131 pts. (74%) Trivedi 2003 No data communicated n = 2266 Number taken from the forest plot	Latham 2003 60 on 114 pts. Sanders 2010 769 on 1125 pts. (68.4%) Trivedi 2003 No data communicated n = 2250 Number taken from the forest plot	Latham (2003) RR = 1.14 (0.80-1.62) **Conclusion: no significant difference between VitD3 and PL.** Sanders (2010) RR = 1.16 (1.05-1.28) **Conclusion: outcome favours PL : P < 0.003** Trivedi (2003) RR = 0.93 (0.77-1.13)

Table 55: ***clinical evidence profile table for vit D versus placebo in community-dwelling patients***

6.5.1.2. Characteristics of included studies in the above mentioned meta-analysis, from evidence profile

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Latham 2003 MC RCT Follow-up 6 months	Inclusion • ≥ 65 years • Evaluated for frailty (cf. ADL) Exclusion – Patients considered not frail – Patients with poor prognosis (life expectancy < 6 months) – Severe cognition impairment (< 20 MMSE) – Physical limitations	– N = 486 – Age: 77-81 – Gender: 53% women – Vitamin D status: 15-21 ng/ml – Bone status: not measured – Dietary Ca intake: not reported – Concomitant medication: not reported	Two by two factorial treatment • Resistance exercise • Attention control • VitD3: 1 dose of 300,000 IU per os • Placebo Resistance exercise Quadriceps exercise during 10 weeks Attention control Telephone calls and home visits + advice	• **ALLOCATION CONCEALMENT**: adequate • **RANDOMISATION:** Adequate (computerized central randomization scheme; stratified block randomization with n=6) • **BLINDING:** Participants/assessors: adequate • **FOLLOW-UP:** • Lost-to follow-up: 444 of 486 patients completed the study • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: • **SELECTIVE REPORTING:** yes/no • **Other important methodological remarks** • - power calculation made: number of patients = adequate
Sanders 2010 SC DB Pl C Follow-up 3 to 5 years	Inclusion Higher risk hip fracture: maternal hip fracture; past fracture; self-reported falling Exclusion Living in high level care facility Albumin corrected Ca-level > 2.65 mmol/l Creatinine Cp > 150 µmol/l Currently taking Vit D > 400IU/d On calcitriol or antifracture therapy	N = 2256 (placebo = 1127; Vit D = 1131) Mean age: 76 years Gender: only women Cp Vit D3 mean 45 (placebo); 53 nmol/l	Control Placebo yearly Intervention Vit D 500,000 IU yearly per os • For 3 to 5 years	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Participants and study staff blinded: adequate. • **FOLLOW-UP:** • Lost-to follow-up: N=2 • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: neutral • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • Power calculation • Ca-intake subgroups

Trivedi 2003 R DB C Follow-up 5 years	<u>Inclusion</u> Men and women Age 65 – 85 years <u>Exclusion</u> People already taking Vit D Contra-indications for Vit D	N = 2686 Mean age: 75 Gender: 649 women; 2037 men Physical activity: active/moderately active between 86,9 and 88,8 % No Vit D status No bone status	<u>Control</u> Placebo <u>Intervention</u> • Vit D 100,000 IU every 4 months	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate stratification by age and sex • **BLINDING:** Participants and investigators: • adequate • **FOLLOW-UP:** not communicated • **ITT:** yes • **FUNDING**: no company funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • Compliance measured: 76% had 80% compliance • No difference between groups

Table 56: characteristics of included studies in above-mentioned meta-analysis from evidence profile

6.5.1.3. Non-habitual schedules of vitamin D versus placebo

Vitamin D3 versus Placebo in non-habitual dosing schedule			
Bibliography: meta-analysis GILLESPIE et al. 2012[3]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	2501 (2) 6 months to 5 years follow-up	RR = **1.14 (1.03-1.27)** ***Statistically significant***	⊕⊕⊕⊖ **MODERATE** All studies are RCT: +4 No concern about study quality: no change in rating The results of both studies differ. The largest study prevails in the outcome: -1 Directness: all studies used high intermittent doses of VitD3: no change in rating Imprecision: no change in rating
Number of fallers	4416 (3) 6 months to 5 years follow-up	RR = **1.08 (0.93-1.26)** NS	⊕⊕⊕⊖ **MODERATE** All studies are RCT: +4 No concern about study quality: no change in rating The results of both studies differ. The largest study prevails in the outcome: -1 Directness: all studies used high intermittent doses of VitD3: no change in rating Imprecision: no change in rating

Table 57: summary and conclusions

Comments

Patients taken to the studies had a mean age of 70+ and were predominantly women. They were not consistently characterized over the studies with regard to vitamin D status, physical activity, bone mineral density concomitant medicines and dietary calcium intake. When vitamin D status was reported, the majority of the patients was deficient. The number of patients taken into the study does not always correspond to the number in the forest plot: e.g. Latham et al. (2003)[82]: 243 patients included i.o. 222 (forest plot). In this study there were 11 deaths in the intervention group vs. 3 in the control group; Trivedi et al. (2003)[56]: the number of patients throughout the study is 2686 i.o. 2038 (forest plot).
The dose of vitamin D was given intermittently. Single shots were at least 100,000 IU (over 4 months) to up to 500,000 IU as a single yearly dose.
Trivedi et al. (2003)[56] do not report the number of fallers, but only the RR.

Conclusion

Treatment with vitamin D compared to placebo, in a schedule consisting of one dose of at least 300,000 IU or more per year, significantly heightens the rate of falls in community-dwelling populations.
Grade : MODERATE quality of evidence

Treatment with vitamin D compared to placebo, in schedule consisting of at least one dose of 100,000 IU every 4 months, does not significantly reduce the rate of fallers in community-dwelling populations.
Grade : MODERATE quality of evidence

6.5.2. Comparison of different doses of vitamin D on top of calcium supplementation in community dwelling patients

6.5.2.1. Rate of falls and number of fallers in community dwelling patients

<table>
<tr><th>Ref</th><th>Comparison:</th><th colspan="2">Results</th><th></th></tr>
<tr><td>Gillespie 2012[3]</td><td>Vit D3 + Ca vs Ca</td><td>Intervention with 2000 IU VitD3 per day
Mean (SD) or event rate</td><td>Intervention with 800 IU VitD3 per day
Mean (SD) or event rate</td><td>RR (95% CI)</td></tr>
<tr><td colspan="5">Rate of falls: no studies</td></tr>
<tr><td colspan="2" rowspan="2">Bischoff-(2010)[83]</td><td colspan="2">N = 1 (number of studies)
n = 173 (number of patients)</td><td rowspan="2">RR not given.
Colecalciferol treatment, 2000 vs 800 IU/d, did not reduce falls (28%; 95% CI, −4% to 68%), but reduced the rate of hospital read-missions by 39% (95% CI, −62% to −1%).

No additional Cochrane evaluation</td></tr>
<tr><td>1.63 falls / patient / year</td><td>1.25 falls / patient / year</td></tr>
<tr><td colspan="5">Number of fallers</td></tr>
<tr><td colspan="2">Bischoff-(2010)[84]</td><td colspan="2">No data on number of fallers given.</td><td></td></tr>
</table>

Table 58: clinical evidence tables for different vitamin D regimens in community-dwelling patients

6.5.2.2. Characteristics of studies with as outcomes rate of falls and number of fallers in community dwelling patients

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Bisschoff-Ferrari 2010 RCT Physio-therapy VitD 12 month follow-up Mean follow-up 312 days	Inclusion • Post restoration of hip fracture • ≥ 65 years • MMSE ≥ 15 Exclusion • Metastatic cancer or • Chemotherapy last year • Serious visual or hearing impairment • Creatinine clearance < 15 ml/min • Kidney stone(s) past 5 years • Primary hyperparathyroidism	• N =173 * Mean age: 84 * Gender distribution: only women * Vitamin D status at baseline: only 8 patients > 30 ng/ml * Bone status: no data * Calcium intake monitoring: participants maintained their own diet (no further details given) * Concomitant medication: no data available	4-arm study • 2000 IU/d VitD3 + standard physiotherapy • 2000 IU/d VitD3 + extended physiotherapy • 800 IU/d VitD3 + standard physiotherapy • 800 IU/d VitD3 + extended physiotherapy Physiotherapy • Standard physiotherapy = 30 min instruction • Extended physiotherapy = 30 min instruction + 30 min home program Ca-supplement 500 mg Ca-carbonate 2x/d for all participants	• **ALLOCATION CONCEALMENT**: adequate • **RANDOMISATION:** computer randomization, double-blinded for VitD3, single-blinded for physiotherapy (adequate) • **BLINDING:** assessing blinded physiotherapist (adequate) • **FOLLOW-UP:** • Lost-to follow-up: 55 patients • Drop-out and Exclusions: see Lost-to-follow-up • Described: yes • Balanced across groups: yes • **ITT:** yes (multivariate analysis) • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks**: MMSE: relatively low values enrolled • Large majority of patients deficient in VitD3

Table 59: characteristics of included studies in above-mentioned meta-analyses from clinical evidence profile

6.5.2.3 Summary and conclusions for different regimens of vitamin D in community-dwelling patients

Different vitamin D doses (2000 IU vs 800 IU)			
Bibliography: meta-analysis GILLESPIE et al. 2012[3]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	n = 173 (1) Follow-up of 12 months	RR = not given Reduction of rate of falling :28%; (95% CI, −4% to 68%) ***NS***	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Only one RCT: +4 Quality: no change in rating Consistency: only one study: -1 Directness: only one study with different dose regimens: -1 Imprecision: relatively low number of patients: -1
Number of fallers	n = 173 (1) Follow-up of 12 months	RR = not given	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Only one RCT: +4 Quality: no change in rating Consistency: only one study: -1 Directness: only one study with different dose regimens: -1 Imprecision: relatively low number of patients: -1

Table 60: summary for different regimens of vitamin D

Comments

The study was not included in the forest plot of the Cochrane analysis (Gillespie et al. 2012). With a mean age of 84, the patients included can be considered as being a group at constitutional risk. Only women were included with vitamin D deficiency (only 8 women on a total of 173 had a normal plasma level of vitamin D). There were no data about bone mineral density, daily calcium intake and concomitant medication.
The daily supplementation with calcium is representative for ambulatory practice. The daily doses of vitamin D (800 and 2000 IU) were sufficiently different to dress a dose-response relationship.
The number of falls was not influenced by enhancing the dose of vitamin D, although there was a lower number of hospital admissions with 2000 IU as compared to 800 IU. In contrast with vitamin D, extended physiotherapy reduced the number of falls.

Conclusion

Treatment with a regimen of 2000 IU versus 800 IU of vitamin D3 did not significantly reduce the rate of falls.
GRADE : VERY LOW level of evidence

6.5.3. Non-habitual schedules of vitamin D3 versus placebo in institutionalized patients

The meta-analysis did not contain results about this specific intervention and population. The search yielded no additional studies.

6.5.4. Comparison of different doses of vitamin D on top of calcium supplementation in institutionalized patients

The meta-analysis did not contain results about this specific intervention and population. The search yielded no additional studies.

6.6. Vitamin D and calcium versus placebo, calcium or other treatments

6.6.1. Vitamin D and calcium versus placebo, calcium or other treatments in community-dwelling patients

These are the pooled results of all aforementioned studies concerning community-dwelling patients. Data was extracted from the forest plot in the Cochrane analysis by Gillespie et al. (2012)[3].

Vitamin D and Ca versus placebo, calcium or other treatments			
Bibliography: meta-analysis GILLESPIE et al. 2012[3]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	N = 9324 (7) Follow-up of 6 months to 5 years	RR = 1.00 (0.90-1.11) ***NS***	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Not all trials were randomized, controlled and double blind: +3 Quality: no change in rating Consistency: only one study lead to positive results, all other studies were consistent: no change in rating Directness: important differences in intervention: cole- and ergocalciferol, different doses, different therapeutic regimens and one study using injections: -1 Imprecision: important differences in the number of patients between the studies: -1
Number of fallers	n = 26747 (13) Follow-up of 6 months to 5 years	RR = 0.96 (0.89-1.03) ***NS***	⊕⊖⊖⊖ **VERY LOW EVIDENCE** Not all trials were randomized, controlled and double blind: +3 Quality: no change in rating Consistency: only one study lead to positive results, all other studies were consistent: no change in rating Directness: important differences in intervention: different doses, different therapeutic regimens and one study using injections: -1 Imprecision: important differences in the number of patients between the studies: -1

Table 61: summary for vitamin D and calcium versus placebo, calcium or other treatments in community-dwelling patients

6.6.2. Vitamin D and calcium versus placebo, calcium or other treatments in institutionalized patients

Data was extracted from the forest plot in the Cochrane analysis by Cameron et al. (2012)[4] and are the pooled results of all aforementioned studies concerning institutionalized patients.

Vitamin D and Ca versus placebo, calcium or other treatments			
Bibliography: meta-analysis CAMERON et al. 2012[4]			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Rate of falling	n = 4603 (5) 12 weeks to 2 years or until discharge from hospital	RR = 0.63 (0.46-0.86) ***SS***	⊕⊖⊖⊖ **VERY LOW EVIDENCE** All trials were randomized, controlled and double blind: +4 Quality: no change in rating Consistency: only one study lead to negative results; all other studies gave a positive outcome in the intervention group; although pooling of the vitamin D2 with a positive outcome led to negative results: -1 Directness: important differences in intervention: cole- and ergocalciferol, different doses, different therapeutic regimens and one study using a multivitamin complex: -1 Imprecision: important differences in the number of patients between the studies: -1
Number of fallers	N = 5186 (6) 12 weeks to 2 years or until discharge from hospital	RR = 0.99 (090-1.08) ***NS***	⊕⊕⊖⊖ **LOW EVIDENCE** All trials were randomized, controlled and double blind: +4 Quality: no change in rating Consistency: no positive outcomes in the intervention group: no change in rating Directness: important differences in intervention: cole- and ergocalciferol, different doses, different therapeutic regimens and one study using a multivitamin complex: -1 Imprecision: important differences in the number of patients between the studies: -1

Table 62: summary for vitamin D and calcium versus placebo, calcium or other treatments in institutionalized patients

Conclusion

Treatment with vitamin D and calcium versus placebo, calcium or other treatments did not significantly reduce the risk of falling for people living in the community.
Grade : VERY LOW level of evidence.

Treatment with vitamin D and calcium versus placebo, calcium or other treatments did not significantly reduce the number of people falling for people living in the community.
Grade : VERY LOW level of evidence

Treatment with vitamin D and calcium versus placebo, calcium or other treatments did significantly reduce the risk of falling for people living in in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade : VERY LOW level of evidence

Treatment with vitamin D and calcium versus placebo, calcium or other treatments did significantly reduce the number of people falling for people living in in nursing homes for the elderly, specialised care apartments or otherwise institutionalised.
Grade : VERY LOW level of evidence

6.7 Detailed critique of the overall evidence

6.7.1 General comments on the evidence from the meta-analyses

The purpose of the literature analysis is to evaluate the level of evidence for the use of vitamin D and calcium in prevention of falling. Research questions are related to the translation of literature in daily practice. To make the evaluation the report focuses on 3 aspects:

Patients
Intervention
Outcome

Patients
For remarks on patients and population, we refer readers to the critical reflections of the literature group (section 2.1)
Some extra remarks however are useful for falling specifically: for community dwelling patients falling is also dependent upon local risk management. This aspect the reader is poorly presented in the included studies. As a consequence, quite a lot of hidden risk factors are taken into the studies and are not corrected for.
This hinders the investigation of the real, actual influence of vitamin D. Furthermore, taking into account the influence of calcium becomes more difficult when patients are taking a daily portion of calcium-containing food. Physical activity is another variable to be taken into account.
The number of patients may strongly vary from study to study. Studies with less than 100 patients and more than 2000 patients are combined and the weight of each study is given in the meta-analysis.

Intervention
For general remarks on interventions, we refer readers to the critical reflections of the literature group (section 2.2)
In the studies in these meta-analyses, there are different substances being used and pooled together (cholecalciferol, ergocalciferol). The galenic form also differs between studies. The evaluation is concentrated on oral intake, but vitamin D injections are also seen.
Monotherapy with vitamin D is sometimes done with intermittent high doses (100,000 IU to 500,000 IU). However, when combined with calcium, daily dosing is preferred in clinical trials.

In the studies in these meta-analyses, there are different substances being used and pooled together (cholecalciferol, ergocalciferol). The galenic form also differs between studies. The evaluation is concentrated on oral intake, but vitamin D injections are also seen.
Monotherapy with vitamin D is sometimes done with intermittent high doses (100,000 IU to 500,000 IU). However, when combined with calcium, daily dosing is preferred in clinical trials.

Duration of studies varies from 6 months to 5 years. Although studies of longer duration are preferable in order to obtain stronger evidence, compliance is often a problem in studies lasting for years. Some studies report high compliance rates of above 90%. Others consider 50% or more as sufficiently reliable. Studies with an open design are more robust with regard to the number of drop-outs.

Outcome
Interventions with vitamin D, vitamin D + calcium or calcium alone do not lead to a lower rate of falls in community dwelling patients. They also do not lower the number of fallers. It must be emphasized that variable therapeutic regimens are combined to obtain these results. Some of those interventions lower the rate of falls in institutionalized patients, but not the number of patients falling.
Subgroup analysis for the pooled results across different interventions was focused on the level of physical activity, the status of vitamin D and compliance. This subgroup analysis gave more positive results, but the studies were not powered to enable direct conclusions. Nevertheless they can be used as valuable information to set up new trials.

6.7.2 Reflections from additional meta-analyses as suggested by the reading committee

Fall prevention in general
The meta-analysis by Vlaeyen et al. 2015[85] which we discuss here was not a result of the search but was suggested by the reading committee. The literature group estimated that reporting results from this MA held an added value for the interpretation of the evidence.

Vitamin D and calcium are not the only interventions that can be made to prevent falls in elderly persons. This systematic review and meta-analysis of 14 randomized controlled trials investigates different fall prevention strategies together. It failed to reveal a significant effect on falls or fallers in institutionalized patients (Vlaeyen et al. 2015)[86].

Patients were staying in nursing homes and were followed during at least 6 months. The studies differed with regard to the preventive measures taken: exercise, medication (mostly medication review; only one study focused on an ergocalciferol supplement), orthostatic hypotension, environment, hip protectors, vision, feet and footwear; and goal setting, reminders and feedback. The definition of a fall was defined in eight studies, but only in one study was the definition clearly explained to the staff collecting and reporting the data. Outcome assessors were blinded in four studies, whereas eight studies used intention-to-treat analysis.
Two multifactorial studies showed a significant decrease in falls over a 12 month period for the intervention groups (minus 36% and 45% respectively). In one study the effect was only significant in cognitively impaired patients and not in cognitively intact residents. When the results of 10 studies were pooled no effect was seen on the number of falls. Pooled data analysis of four studies showed a significant effect of intervention on recurrent falls and a non-significant effect on the number of fallers.

Differences in meta-analyses
A meta-analysis commissioned by the Endocrine Society (ES) reported that vitamin D with or without calcium supplements, reduced the odds of falling by 14% in a pooled analysis of 25 randomized controlled trials (Murad et al. 2011)[87]. Most of those interventions however were with vitamin D and calcium together. This review also pools both vitamin D3 and vitamin D2 interventions together.

The two Cochrane analyses used as source documents in the consensus literature analysis reported no effect of vitamin D with or without calcium in community dwelling patients, whereas the effect was only significant for the rate of falling, but not on the number of fallers, in institutionalized patients.

A 2009 meta-analysis of eight RCT's reported that fall prevention occurred with high-dose vitamin D and achieved 25-hydroxyvitamin D greater than 60 nmol/L (Bischoff-Ferrari et al. 2009[88]), but a subsequent Institute of Medicine report criticized the methodology used and reanalysed the same data, concluding that neither vitamin D supplements nor higher level of 25-hydroxyvitamin D prevented falls (Institute of Medicine 2011).

Bolland et al. (2014)[89] extracted data from 25 randomized controlled trials included in the ES meta-analysis. They calculated the treatment effect for each trial, compared them with the published ES meta-analysis and determined the reason for any difference. The Bolland reanalysis resulted in a non-significant 5% risk reduction of falling which is only of marginal clinical importance.
The authors identified several reasons for differences between analyses.

- As falls data were not always available, falls data were deducted from fracture data (equating a fall with a fracture), which leads to an underestimation.
- The number of falls was rounded-up differently.
- The number (of patients) used to calculate the outcomes was not always consistent. Sometimes another number is found in the meta-analysis than in the original study. Even if the numerator is the same, a change in denominator can influence the RR.
- Not the whole set but a subset (e.g. only women) of trial data was analysed.
- The trial data were split by gender.
- Sometimes only falls that did not cause fracture were used.

In regard to falls and its connection to fractures, other factors are important like osteoarthritis and knee pain. They could influence the severity of falls and subsequent fractures but not necessarily the number of falls (see Arden et al. (2006)[90])

Bolland et al. (2014[89]) conclude that methodological differences in utilizing data from the same trials directly led to different conclusions between meta-analyses on the efficacy of vitamin D supplements on falls. They are in favour of clearly explaining methodological issues when making meta-analysis.

7. Results: Cardiovascular safety of calcium

Our search focused on endpoints related to general cardiovascular and heart disease. However, as said in the critical reflections of literature group and reading committee, calcium also has effects on for example blood pressure.

Results varied a lot, some studies identify a statistically significant risk, others don't, and meta-analyses also do not give a conclusive answer.

We took one meta-analysis by Bolland et al (2010)[7] that did conclude to a heightened risk of myocardial infraction, and one by Lewis et al (2014)[8] that did not find a cardiovascular risk for calcium and compared both. The article by Bolland et al. has raised a high number of remarks and responses from other authors, the article by Lewis et al, being newer, hasn't generated as much. An overview of the objections raised to the article by Bolland and the authors' reply can be found in an article by Reid and Bolland[91].

The major critiques on the article by Bolland et al. are the following:

Critique	Reply from author group
Cardiovascular events were not primary study endpoint	The data on these outcomes was indeed not gathered in a standardized manner. However the magnitude of the increased risk of MI was consistent across trials and the likelihood of differential misclassification or misreporting is small since selected trials were blinded and placebo-controlled.
Adverse effects might be restricted to subgroups	There was no interaction between age, gender, baseline vitamin D status or type of supplement used and risk of MI. There is an interaction between dietary calcium and the risk of MI but not the other endpoints.
The increase in risk of MI is not accompanied by increased mortality	10-20% of individuals died from having a MI, so a 30% increase in MI found with calcium use should result in a 3-6% increase in mortality. The study did not have the power to detect effects of that magnitude.
Studies co-administering calcium and vitamin D are excluded	This argument is persuasive if a specific mechanism by which vitamin D might reverse the calcium effect can be identified or if there is trial data suggesting an interaction.
Lower doses of calcium supplement might be adequate (dietary intake + supplements give a mean total intake of around 1800 mg/day)	Evidence from clinical trials and observational data both suggest the skeletal effects of calcium alone are small, an evidence of benefit has only been demonstrated in trials using doses such as those in the meta-analysis.

Another important remark is that the article by Lewis et al (2014) only analyses data from women, and if the trial comprised a mixed population, only the data on women was included in the MA. The article by Lewis et al. (2014)[8] also looks at different endpoints than the one by Bolland et al. (2010)[7].

A last remark is that the two meta-analyses pool both trials with calcium as intervention and trials with calcium and vitamin D.

Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis by Bolland M. et al.
March 2010

Search strategy
Searched, in November 2007 Medline, Embase and the Cochrane Central Register of Controlled Trials for randomised placebo controlled trials of calcium supplements, using the terms "calcium", "randomised controlled trial", and "placebo" as text words, and corresponding MeSH terms (full details available from the authors). They searched for studies in the reference lists of meta-analyses published between 1990 and 2007 for the effect of calcium supplements on bone density, fracture, colorectal neoplasia, and blood pressure, and in two clinical trial registries (ClinicalTrials.gov and Australian New Zealand Clinical Trials Registry). No language restrictions were applied. Update of the electronic database searched in March 2010.

Inclusion criteria
– RCT
– placebo-controlled
– Elemental calcium at a dose of ≥500 mg / day (Dose of at least 1000 mg / day in 10 out of 11 trials included)
– Participants mean age at baseline > 40 years (average age 73 years, 83% were women)
– 100 or more participants randomised
– Trial duration more than one year

Endpoints:
- Primary: Time to first MI, time to first stroke, time to first event for composite endpoint of myocardial infarction, stroke or sudden death
- Secondary: time to death

The effects of calcium supplementation on verified coronary heart disease hospitlization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials
by Lewis J. et al.
July 2014

RCTs with and without vitamin D were identified through Cochrane Central Register of Controlled Trials (1970 to 2013), MEDLINE (1966 to 2013), EMBASE (1974 to 2013) and reference lists. Additionally, studies identified from reviews and meta-analyses and their reference list were included. The last update of the search was performed on 24 may 2013. Two search strategies were used. The preliminary search was limited to: human, RCT in the English language for trials meeting the inclusion criteria, intervetnion terms, “calcium”, “calcium supplementation”, “vitamin D”, “ergocalciferol”, “cholecalciferol”, “calcitriol”, and outcomes terms including “vascular disease, cardiovascular disease, myocardial infarction, coronary heart disease, coronary artery disease, mortality, death. Additional searches were performed after the initial search using combinations of the intervention terms without outcome terms because some trials did not report cardiovascular or mortality outcomes as primary endpoints or search keywords.

Inclusion criteria
-Individual or cluster RCT
- Groups differed only by calcium supplementation with or without vitamin D, or with or without vitamin D and a factor unlikely to affect coronary heart disease
- Dose of calcium higher than 500 mg / day
- More than one year
- Mean age of the cohort: over 50, only figures for women were considered
- Outcomes verified by clinical review, hospital discharge record or death certificate

Endpoints
- Primary: CHD (including, but not limited to MI), all-cause mortality.

7.1 Clinical evidence profile from meta-analyses

Ref	Comparison:	Results		
Bolland 2010[7] & Lewis 2014[8]	**Ca (with or without vitamin D) compared to no calcium**	**Ca with or without vitamin D** Mean (SD) or event rate	**No calcium** Mean (SD) or event rate	**RR (95% CI)**
BOLLAND: Myocardial infarction				
Baron 1999[92], Grant 2005[43], Grant 2005 vit D[43]*, Prince 2006[44], Reid 2006[36], Lappe 2007[93], Reid 2008[94]		Total (N = 6, n = 10,210)		RR = 1.27 (1.01 – 1.59) ***SS***
		166 / 5205	130/5005	
LEWIS: Myocardial infarction				
Grant 2005[43], Grand 2005 vitD[43]* Jackson 2006 (WHI)[32], Lappe 2007[93], Larsen 2004[95], Prince 2006[44], Reid 2006[36], Sambrook 2012[96]		Total (N = 7, n = 51,111)		RR = 1.08 (0.93 – 1.25) *NS*
		584 / 25908	539 / 25203	
BOLLAND: Stroke				
Reid 1993[37], Baron 1999[92], Grant 2005[43], Grant 2005 vit D[43]* Prince 2006[44], Reid 2006[36], Bonnick 2007[97], Lappe 2007[93]		Total (N = 7, n = 10,584)		RR = 1.12 (0.92 – 1.36) *NS*
		211 / 5338	190 / 5246	
BOLLAND: MI, stroke or sudden death (composite)				
Reid 1993[37], Baron 1999[92], Grant 2005[43], Grant 2005 vit D[43]*, Prince 2006[44], Reid 2006[36], Lappe 2007[93], Reid 2008[94]		Total (N = 7, n = 10345)		RR = 1.12 (0.97 – 1.30) *NS*
		358 / 5272	319 / 5072	
BOLLAND: all-cause mortality / death				
Baron 1999[92], Grant 2005[43], Grant 2005 vit D[43]*, Prince 2006[44], Reid 2006[36], Lappe 2007[93], Reid 2008[94]		Total (N = 6, N = 10,210)		RR = 1.07 (0.95 – 1.19) *NS*
		559 / 5205	535 / 5005	
LEWIS: all-cause mortality / death				
Bonnick 2007[97], Brazier 2005[98], Baeksgaard 1998[99], Chailurkit 2010[100], Chapuy 1992[61], Chapuy 2002[62], Grant 2005[43], Grant 2005 vit D[43]*, Harwood 2004[49], Jackson 2006 (WHI)[32], Krieg 1999[101], Larsen 2004[95], Porthouse 2005[65], Prince 2006[44], Reid 2006[36], Riggs 1998[40], Salovaara 2010[64], Sambrook 2012[96]		Total (N = 17, N = 62,383)		RR = 0.96 (0.91 – 1.02) *NS*
		2053 / 31,108	2104 / 31275	
LEWIS: CHD				
Grant 2005[43], Grant 2005 vit D[43]*, Jackson 2006 (WHI)[32], Larsen 2004[95], Prince 2006[44], Sambrook 2012[96]		Total (N = 5, n = 48,460)		RR = 1.02 (0.96 – 1.09)T *NS*
		1720 / 24284	1670 / 24176	

Table 63: clinical evidence profile for CV safety of calcium

***Grant 2005 vit D is the same study as Grant 2005 but with the vit D arms considered apart. Detailed numbers are given in the source documents, and totals have been calculated so that we do not count the same patient twice. Grant 2005 and Grant 2005 vit D are counted together as being only one study, not two.

7.2. Characteristics of included studies in above mentioned meta-analyses

From Bolland M. et al., 2010

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Baron 1999[92] Study design: RCT DB Follow up: 4 years Patient-level data provided on cardio-vascular outcomes	**<u>Inclusion criteria:</u>** - histologically confined large bowel adenoma removed within three months of recruitment - less than 80 years old - in good health **<u>Exclusion criteria:</u>** - polyposis syndrome - invasive large bowel cancer - malabsorption syndromes - condition that might be worsened with additional calcium	N = 930 **Mean age**:58 years **Gender distribution**: 100% women **Vitamin D status at baseline:** Mean serum 25(OH)D: 73(±27) nmol/l **Bone status (osteoporosis, BMD, previous fractures?):** not relevant in original study design **Dietary calcium intake monitoring**: assessed by validated food frequency questionnaire 877 ± 437 mg / day **Concomitant medication**: assessed by questionnaire, data not shown calcium supplements before study entry: 3% (discontinued)	1) 1200 mg of calcium (as Ca carbonate) *(n=464)* 2) placebo *(n = 466)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Unclear, states double blind, no precisions • **LOST TO FOLLOW-UP:** placebo: 1.5%; intervention: 2,2% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: neutral funding • **SELECTIVE REPORTING:** no • **Important methodological remarks**: placebo-run-in • **Primary endpoint:** risk of recurrent colorectal adenomas (lower risk of recurrent adenomas in patients with calcium RR=0.81 (95% CI: 0.60 - 0.99))

Bonnick 2007[97] Study design: RCT DB MC Follow up: 2 years Data on CV-outcomes: trial-level	**<u>Inclusion criteria:</u>** - community-dwelling women - post-menopausal - in general good health - ≥45 years old and ≥5 years post-menopause - ≥18 years old and ≥5 years surgical menopause - L1-L4 BMD ≥2 SD below peak BMD **<u>Exclusion criteria:</u>** - metabolic bone disease - bilateral hip replacement - rheumatoid arthritis - iron-deficiency anaemia requiring treatment with iron - any sever malabsorption syndrome - uncontrolled hypertension - a history of calcium urolithiasis - angina or myocardial infarction	N = 701 **Mean age**: 66.2 ± 8.8 years **Gender distribution**: 100% female **Vitamin D status at baseline**: not measured **Bone status** (osteoporosis, BMD, previous fractures?): L1-L4 BMD ≥2 SD below peak BMD **Dietary calcium intake monitoring:** Daily dietary calcium ≥ 800 mg Mean: 1240 (±580) mg/day **Concomitant medication**: no data	All group: 400 IU vit D 1) Alendronate 10 mg + calcium placebo (n = 281) 2) Alendronate 10 mg + calcium 1000 mg (n = 282) 3) Alendronate placebo + calcium 1000 mg (n = 96)	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** adequate for participants, rest: Unclear • **LOST TO FOLLOW-UP: 31%** • Described: yes • Balanced across groups: yes • **FUNDING**: Merckx & co. • **Important methodological remarks**: dietary run in and 400 IU vit D / day • **Primary endpoint:** percent change from baseline in BMD in g/cm² of L1-L4. (0.8% higher in patients on calcium alone, 5.6% higher on alendronate alone, 6.0% higher with combination. All differences significant)

Grant / The RECORD trial group 2005[43] Design: RCT DB PL Duration of follow-up: 24 to 62 months Data on cardio-vascular outcomes: Patient-level	**<u>Inclusion criteria:</u>** - osteoporotic fracture in the previous 10 years **Exclusion criteria:** - bed or chair-bound before fracture - cognitive impairment - cancer in the past 10 years with risk of bone metastasis - fracture associated with bone abnormality - hypercalcaemia - renal stone in the past 10 years - life expectancy less than 6 months - individuals known to be leaving the UK - daily intake of more than 200 IU vitamin D or more than 500 mg of Ca supplements - intake in the past 5 years of fluoride, bisphosphonates, calcitonin, tibolone, HRT, SERM, any vitamin D metabolite or vitamin D by injection in the past year	N = 5292 **Mean age:** 77 **Gender distribution** 85% women **Vitamin D status at baseline:** - serum 25(OH)D measured in a subgroup by straight-phase HPLC - mean: 45 (±18)nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** all participants had a previous fracture **Dietary calcium intake monitoring?** Semi-quantitatively assessed by food-frequency questionnaire Mean: 820 (±350) mg/day **Concomitant medication:** data on some medications, like thiazide diuretics, oral steroids or thyroxine	*1) 800 IU vit D3 (n=1343)* *2) 800 IU vit D3 & 1000 mg Ca (n=1306)* *3) 1000 mg Ca vs (n= 1311)* *4) Placebo (n= 1332)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: • 24 months: 8.5% deaths, 1.1% withdrawal • 48 months: deaths 16.3%, 1.2% withdrawal • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: neutral funding + Shire Pharmaceuticals funded the drugs • **SELECTIVE REPORTING:** no • **Primary endpoint**: fractures and falls

Lappe 2007[93] Study design: RCT Follow up: 4 years Data on cardiovascular outcomes: Trial level	**Inclusion criteria** - older than 55 years - absence of known cancers - mental and physical status sufficiently good to permit 4 year participation **Exclusion criteria** no information	N = 1179 **Mean age**: 67 years **Gender distribution**: 100% female **Vitamin D status at baseline**: - baseline serum 25(OH)D: 71.8±20.3nmol/L - radio-immunoassay after extraction with IDS kit **Bone status** (osteoporosis, BMD, previous fractures?): no data **Dietary calcium intake monitoring:** Mean: 1070 mg/day **Concomitant medication**: 46% received oestrogen from their primary physician	1) 1400 mg/d of calcium as citrate OR 1500 mg/day as calcium carbonate + vit D placebo (n = 445) 2) calcium as above + 1000 IU of vitamin D3 (n = 446) 3) matching placebo's (n = 288)	• **ALLOCATION CONCEALMENT**: adequate • **RANDOMISATION:** Adequate • **BLINDING:** adequate for participants, others: unclear • **FOLLOW-UP:** • Lost-to follow-up: 13,2% • Described: no • Balanced across groups: unknown • **ITT:** yes • **FUNDING**: study medication by Mission Pharmaceutical and GlaxoSmithKline, other funding not mentioned • **SELECTIVE REPORTING:** no • **Primary endpoint**: skeletal status and calcium economy

Prince 2006[44] Study design: RCT PL Follow-up: 5 year Data on cardiovascular outcomes: trial level	**Inclusion criteria:** women ≥ 70 years ambulatory = community-dwelling **Exclusion criteria:** - Medical conditions that made it unlikely patients would survive the 5 years of study - participating in another clinical trial - medication that could affect bone mass	N = 1460 **Mean age:** 75 y **Gender distribution:** 100% women **Vitamin D status at baseline:** measured in a subset using an extraction technique, followed by a competitive binding assay using diluted human serum that measures 25-hydroxycholecalciferol and ergocalciferol levels equally Generally above deficiency level, no further information **Bone status (osteoporosis, previous fractures? BMD?)** Prevalent fractures (at ≥50y) recorded (approx. 25%) Both 1° and 2° prevention **Calcium intake monitoring?** Food-frequency questionnaire Mean: 915 mg/day **Concomitant medication:** no data	1) *1200 mg/day calcium as calcium carbonate (n = 730)* *2) placebo (n=730)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Participants Adequate • personnel/assessors: Unclear • **FOLLOW-UP: Not described** • **ITT:** censored for death and withdrawal + another PPA • **FUNDING**: neutral • **SELECTIVE REPORTING:** no • **Primary end point**: Fracture incidence. (main finding: no significant difference except in patients who took <80% of tablets)

Reid 1993[37] Design: RCT PL Duration of follow-up: 2 years Data on CV outcomes: patient-level data	**Inclusion criteria:** - Post-menopausal women (3 or more years after menopause) - mean dietary calcium intake of 750 mg/day **Exclusion criteria:** - History of disorders of calcium metabolism (including symptomatic vertebral fractures) - Renal, thyroid or hepatic dysfunction - Current systemic disease - HRT in the previous 3 years - Use of supraphysiologic doses of glucocorticoid for >6m - Current use of glucocorticoids, thiazide diuretic or anticonvulsant medication	N = 130 **Mean age**: 58 **Gender distribution**: 100% women **Vitamin D status at baseline**: - known, method not given - serum 25(OH)D mean: 93 (±37) nmol/l **Bone status** (osteoporosis, previous fractures?) BMD reported **Dietary calcium intake monitoring?** Assessed by four day diet diaries, mean dietary intake of 750 mg **Concomitant medication?** No data	*1) 1000 mg / day Calcium (n= 68)* *2) Placebo (n= 67)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear, merely states "randomly assigned" • **BLINDING:** Adequate for participants, unclear for assessors • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 6.2% • Described: only the reason for stopping the study • Balanced across groups: unknown • **ITT:** no, only takes into account the 122 women who finished the study • **FUNDING**: Health research council of new zealand, tablets provided by Sandoz • **SELECTIVE REPORTING:** no • **Primary end point**: bone mineral density

Reid 2006[36] Design: RCT PL DB Duration of follow-up: 5 years Data on CV outcomes: patient-level data	**Inclusion criteria:** - more than 55 years, post-menopausal - not receiving therapy for osteoporosis or taking calcium supplements - free of major ongoing disease - Lumbar spine density not below the age-appropriate normal range **Exclusion criteria:** **- c**reatinine more than 2.3 mg/dL - serum 25-hydroxyvitamin D was lower than 10 µg/L (25 nmol/L)	N = 1471 **Mean age:** 74 years **Gender distribution:** 100% women **Vitamin D status at baseline:** - see exclusion criteria - measured by radio-immunoassay - serum 25(OH)D mean: 54 (±18) nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** primary prevention only, (patients were switched to bisphosphonates or other after fracture) **Calcium intake monitoring?** Yes - mean intake placebo: 853 mg/d - mean intake intervention: 861 mg/d **Concomitant medication:** unknown	*1) 1 g of Ca/day as Calcium citrate (n=732)* *2) placebo* • *(n=739)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate, participants and assessors • **LOST TO FOLLOW-UP: 10%** • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: undisclosed • **SELECTIVE REPORTING:** no • **Other important methodological remarks**: power calculation would be adequate to detect a 40% decrease in fracture rate • Low compliance over the entire study (58% in placebo group, 55% in verum group) • **Primary end point**: clinical fractures

Reid 2008[94] Study design: Follow-up: Data on CV outcomes: patient-level	**Inclusion criteria:** - men - aged at least 40 years - in good general health **Exclusion criteria:** - any major active disease (including coronary heart disease) - hypertension - diabetes mellitus - untreated hypothyroidism, liver disease, malignant lesion or metabolic bone disease - estimated 5-year risk cardiovascular risk of more than 15% - serum creatinine levels higher than 0.002 mg/dL, - serum 25(OH)D lover than 10ng/ml - lipid-lowering therapy or use of testosterone, anabolic steroids, glucocorticoids or bisphosphonates in the previous year - lumbar spine or total hip BMD Z-score lover than -2	N= 323 **Mean age:** 56 years **Gender distribution:** 0% female **Vitamin D status at baseline:** Serum 25(OH)D mean: 92 (±33) nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** information on BMD given **Calcium intake monitoring?** Mean: 870 (± 450) mg / day **Concomitant medication:** no data	1) 600 mg / day of calcium as calcium citrate (n = 108) 2) 1200 mg / day of calcium as calcium citrate (n = 108) 3) matching placebo (n = 107)	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Adequate • **LOST TO FOLLOW-UP: 4%** • Described: yes • Balanced across groups: no (more loss in 1200 mg ca group) • **ITT:** yes • **FUNDING**: medication by Mission Pharmacal, Tx., rest of funding from neutral source • **SELECTIVE REPORTING:** no • **Other important methodological remarks**: Placebo-run-in • **Primary end point**: spine bone mineral density (only statistically significant increase in 1200 mg/day group)

Table 64: characteristics of studies included in the meta-analysis by Bolland et al 2010

B. From Lewis et al., 2014

Study details	Inclusion / exclusion criteria	Patients characteristics	Intervention	Study quality
Baeksgaard 1998[99] Study design: RCT Follow-up: 2 years Data on: Mortality	**<u>Inclusion criteria:</u>** - Caucasian background - 58-67 years - good general health - postmenopausal status **<u>Exclusion criteria:</u>** - patients treated with oestrogen or calcitonin during the previous 12 months or with bisphosphonates the previous 24 months were not included in the studies - diseases known to affect bone metabolism - renal disease with serum creatinine above 120 µmol/l - hepatic disease with increased ALAT and/or decreased coagulation factors II, VII, and X - decreased function of the endocrine pancreas	N = 240 **Mean age**: 62 **Gender distribution**: **Vitamin D status at baseline**: no data **Bone status (osteoporosis, BMD, previous fractures?)**: BMD measurements **Dietary calcium intake monitoring**: assessed using 7-day dietary diary mean: 918 mg/day **Concomitant medication**: no data	1) 1000 mg / day of calcium as ca carbonate + 560 IU of vit D3 (n = 80) 2) 1000 mg of calcium as ca carbonate, 560 IU of vitamin D3 and multivitamin supplement (n = 80) 3) placebo (n = 80)	• **ALLOCATION CONCEALMENT**: Unclear, not described • **RANDOMISATION:** Unclear, not described • **BLINDING:** Unclear, not described • Lost to follow up, drop-out and exclusion: 17% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: tablets provided by Lube Ltd., funding undisclosed • **SELECTIVE REPORTING:** yes/no • **Important methodological remarks**: no adherence assessing • **Primary endpoint:** changes in BMD, positive effect
Bonnick 2007[97]	See studies from Bolland 2010			

Brazier 2005[98] Study design: RCT DB MC Follow up: 2 years Data on: Mortality	**<u>Inclusion criteria:</u>** - 25(OH)D levels ≤12ng/mL - women - aged >65 years **<u>Exclusion criteria:</u>** - hypercalcemia - primary hypoparathyroïdism - renal insufficiency - hepatic insufficiency - having received a bisphosphonate, calcitonin, vitamin D or metabolites, estrogen, raloxifene, fluoride, anticonvulsives or any other treatment acting on bone metabolism in the past 6 months	N = 192 **Mean age**: 74.6 years **Gender distribution**: 100% female **Vitamin D status at baseline:** - Vitamin D insufficient (see inclusion criteria) - serum 25(OH)D measured by competitive protein binding assay - mean: 7.0 ng/mL **Bone status** (osteoporosis, BMD, previous fractures?) **Dietary calcium intake monitoring**: by validated food-frequency questionnaire mean intake: 736,0 mg/day C**oncomitant medication**: no data	1) 500 mg of calcium carbonate and 400 IU of vit D3 (n = 95) 2) placebo (n = 97)	• **ALLOCATION CONCEALMENT**: Unclear, not described • **RANDOMISATION:** Adequate • **BLINDING:** Unclear: states double blind, not described • Lost to follow-up, drop-out and exclusion: 26% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: industry funding (Innothera Laboratories) • **SELECTIVE REPORTING:** no • **Primary endpoint:** effect on BMD and biochemical markers of bone restion

Chailurkit 2010[100] Study design: RCT Follow-up: 2 years Data on: mortality	**<u>Inclusion criteria</u>** - women **<u>Exclusion criteria</u>** - history of metastatic or nonosteoporotic metabolic disease - history of kidney stones within previous 5 years - vertebral fractures - thyroid or parathyroid disease - use of calcium or vitamin D supplementation within the previous 2 months - use of HRT or medications influencing bone metabolism within the previous 6 months - use of previous year of glucocorticoid, anticonvulsants or fluoride	N = 336 **Mean age**: 66 years **Gender distribution:** 100% female **Vitamin D status at baseline**: - serum 25(OH)D measured by electrochemiluminescence immunoassay subjects classified according to baseline 25(OH)D levels - mean: 69.05 nmol/l Bone status (osteop, BMD, previous fractures?) **Dietary calcium intake monitoring:** measured by food frequency questionnaire median daily intake in Thais is 360 mg / day **Concomitant medication:** no data	1) 500 mg / day elemental calcium as calcium carbonate (n = 175) 2) placebo (n = 161)	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Personnel, assessor: unclear • participants: adequate • **Lost to follow-up, drop-out and exclusion**: 15,4% • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: tablets provided by British dispensary, assay by Roche diagnostics, rest of funding from neutral source • **SELECTIVE REPORTING:** yno • **Important methodological remarks**: study conducted in the vicinity of Bangkok • **Primary endpoint:** influence of vitamin D status on PTH and BMD

Chapuy 1992[61] Design: RCT DB Duration of follow-up: 18 mo Data on: mortality	**Inclusion criteria:** Elderly women Ambulant (walk indoors with a cane) No serious medical condition life expectancy of at least 18 months **Institutionalised** **Exclusion criteria:** Having received drugs known to alter bone metabolism (corticosteroids,thyroxine...) within the past year Being treated with fluoride salts >3 months or having received Ca or vitamin D treatment during the previous six months or for more than one year the past five years	N = 3270 **Mean age:** 84 (69-106) years **Gender distribution:** 100% women **Vitamin D status at baseline:** - competitive binding-protein assay - mean: 16 ± 11 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** women who had fractures in the past were not excluded **Calcium intake monitoring?** Semi-quantitative assessment mean: 512 mg / day **Concomitant medication:** women taking oestrogen or thiazide diuretic were not excluded	*1) 1200 mg Calcium + 800 IU vitamin D3 (n = 1634)* *2) placebo (n = 1636)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear, states • "the women were randomly assigned to the treatment of the placebo group in groups of four at each nursing home" • **BLINDING:** Adequate • **FOLLOW-UP:** • Deaths: 16 in vit D group; 17% in placebo group • Withdrawal for other reasons: 30% in vit D group; 29% in placebo group • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** • Vertebral fractures not measured

Chapuy 2002[62] Design: RCT DB Duration of follow-up: 2 years Data on: mortality	**<u>Inclusion criteria:</u>** Ambulatory women **Institutionalized** (apartment homes for elderly) Life expectancy of 24 months **<u>Exclusion criteria</u>:** Disease exclusions: intestinal malabsorption, hypercalcaemia (serum calcium > 2.63 mmol/L), chronic renal failure (serum creatinine > 150 µmol/L) Drug exclusions: received drugs known to alter bone metabolism, such as corticosteroids, anticonvulsants or a high dose of thyroxine, in the past year. Fluoride salts (> 3 months), bisphosphonates, calcitonin (> 1 month), calcium (> 500 mg daily), vitamin D (> 100 IU daily) in last 12 months	N = 583 **Mean age:** 85.2 y **Gender distribution: 1**00% female **Vitamin D status at baseline:** -Serum 25(OH)D measured by competitive-binding protein assay - mean: 9,2 ng/ml **Bone status (osteoporosis, previous fractures? BMD?)** - data on BMD given **Calcium intake monitoring?** - Semi-quantitatively assessed by questionnaire, mean : 557 mg / day **Concomitant medication?** Registered, data not given	*1) Calcium 1200 mg as tricalcium phosphate and vitamin D3 800 IU daily as 1 sachet* *2) Calcium 1200 mg as tricalcium phosphate sachet and 2 pills of vitamin D3 400 IU daily* *(groups 1 and 2: n = 389)* *versus* *3) 1 placebo sachet and 2 placebo tablets daily. (n = 194)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** • Participants: Adequate • personnel/assessors: Unclear • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 27.2% separate CA-VitD, 29.1 fixed Ca+vitD, 36.1% placebo • Described: y • Balanced across groups: no • **ITT:** yes • **FUNDING**: Merckx KGaA • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • Combines ca-vit D fixed and separate combo to evaluate global impact of calcium and vit D3 treatment because no biochemical parameter was different. • Not powered to detect a reduction in hip fracture rate
Grant 2005 (Record)[43] Data on: Mortality CHD	See studies from Bolland 2010			

Harwood 2004[49] Design: R No PL Duration of follow-up: 1 year Data on: Mortality	**Inclusion criteria:** - within 7 days of surgery for hip fracture, - community residence - independent in activities of daily living **Exclusion criteria**: - Disease exclusions: institutionalised, diseases known to affect bone metabolism - Abbreviated mental test score < 7 at time of recruitment - Drug exclusions: medications know to affect bone metabolism	N = 150 **Mean age:** 81,2 y **Gender distribution**: 100% female **Vitamin D status at baseline:** - measured by radio-immunoassay - mean: 29 nmol/l (6-85nmol/l) **Bone status** (osteoporosis, previous fractures? BMD?) - all subjects recruited after operation for hip fracture **Dietary calcium intake?** - No data **Concomitant medication?** - No data	*1. Vitamin D2 300,000 IU by injection once at beginning of trial* (n= 38) 2. Vitamin D2 300,000 IU by injection once at beginning of trial and calcium 1000 mg daily as 2 tablets (n= 36) 3. Vitamin D3 800 IU and calcium 1000 mg daily as 2 tablets (n= 39), 4. No trial treatment (n=37)	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Inadequate, no placebo's • **FOLLOW-UP:** • Lost-to follow-up: 20,6 % • Described: yes • Balanced across groups: yes • **ITT:** no • **FUNDING**: Provalis health care**, industry** • **SELECTIVE REPORTING:** no • **Other important methodological remarks** study wasn't blinded, no placebo's • very low number of events for falls (n=11)

Jackson (WHI) 2006[32] Design: RCT Duration: 7 years Data on: Mortality, CHD	**Inclusion criteria:** - 50 to 79 years - no medical condition associated with predicted survival of less than 3 years **Exclusion criteria:** **-** Disease exclusions: hypercalcaemia, renal calculi - Drug exclusions: corticosteroid use, calcitriol use, calcium supplements > 1000 mg/day, vitamin D > 600 IU/day (> 1000 IU/day after 1999)	N = 36,282 **Mean age:** 62,4 years **Gender distribution:** 100% female **Vitamin D status at baseline:** - measured in case-control pairs matching for age, latitude, race and date of venipuncture by DiaSorin - Liaison chemiluminescent immunoassay system **Bone status (osteoporosis, previous fractures? BMD?)** - history of fractures recorded, approx. 10% had a fracture at age ≥ 55 **Calcium intake monitoring?** - Food frequency questionnaire + intake of calcium from supplements **Concomitant medication:** 50% of patients under hormone replacement therapy 20,7% taking alendronate 1,8% taking risendronate 3,0% taking raloxifene 1,2% taking calcitonin	*1000 mg calcium as calcium carbonate + 400 IU vitamin D3 as 2 tablets daily (n = 18176))* *versus* *2 placebo tablets daily (n= 18106)*	• **ALLOCATION CONCEALMENT**:Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up: 2,7% • Drop-out and Exclusions: (deaths) 4,3 % • Described: yes • Balanced across groups: yes • **ITT:** yes • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** recruited among women already enrolled in the WHI dietary modification trial or WHI hormone therapy trial → has an effect on bone • + personal calcium supplements of up to 1000 mg / day and vit D supplements (up to 600 IU then 1000 iu / day) were also permitted

Krieg 1999[101] Study design: RCT Open-label No PL MC Follow-up: 2 years Data on: Mortality	**Inclusion criteria:** - elderly institutionalised women **Exclusion criteria:** - not described	N = 248 (only 103 analysed) **Mean age:** 85 years **Gender distribution:** 100 % female **Vitamin D status at baseline:** - measured by protein-binding assay - mean: 11,8 ng **Bone status (osteoporosis, previous fractures? BMD?)** no data **Calcium intake monitoring?** No data **Concomitant medication** no data	1) 1000 mg of elemental calcium as calcium carbonate and 800 IU vit D3 (n = 124) 2) Matching placebo's (n = 124)	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** No blinding • Lost-to follow-up, drop-outs and exclusions: 58% • Described: yes • Balanced across groups: yes • **ITT:** NO • **FUNDING**: undisclosed • **SELECTIVE REPORTING:** yes • **Important methodological remarks**: no exclusion criteria specified. Measurements made with a uncommon method. Very high drop out rate.
Lappe 2007[93] Data on: MI	See studies from Bolland 2010			

Larsen 2004[95] Study Design: RCT No PL Follow-up: 3 years Data on: Mortality, CHD	**Inclusion criteria:** - community-dwelling residents - aged >65years **Exclusion criteria:** - living in a nursing home - severely impaired persons living in sheltered homes for the elderly - elderly with mental retardation	N = 9605 **Mean age:** 75 years **Gender distribution:** 60.1% female, 39.9% male **Vitamin D status at baseline:** - Serum 25(OH)D measured by competitive radioreceptor assay - measured in a subset - mean: 39 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** Previous fractures known, data given **Calcium intake monitoring?** No data **Concomitant medication:** Assessed, some data given	1) home safety inspection (n = 2532) 2) 1000 mg of elemental calcium as calcium carbonate and 400 IU of vitamin D3+ revision of current pharmaceutical treatment (n = 2426) 3) interventions (1) and (2) combined (n = 2531 4) no intervention (n = 2116)	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Inadequate, randomized by dividing city up in blocks and assigning intervention to block • **BLINDING:** No blinding • Lost-to follow-up, drop-outs and exclusions: • Described: yes • Balanced across groups: yes • **ITT:** "intention to prevent" • **FUNDING**: neutral funding, tablets by nycomed **SELECTIVE REPORTING: no** • **Important methodological remarks:** relatively few events of fractures in men • **Main finding:** Effect of calcium and vitamin D on fracture risk. Significant only in post-hoc defined subgroups.

Porthouse 2005[65] Design: RCT Duration of follow-up: 18 to 42 months median: 24 Data on: mortality	**Inclusion criteria:** - women 70 or older - one or more risk factors for hip fractures: any previous fracture, low body weight, smoker, family history of hip fracture, fair or poor self reported health - living in nursing homes **Exclusion criteria:** - Disease exclusions: kidney or bladder stones, renal failure, hypercalcaemia, cognitive impairment, life expectancy < 6 months - Drug exclusions: current calcium supplementation of > 500 mg/day	N = 3314 **Mean age:** 77 ± 5 years **Gender distribution:** women 100% **Vitamin D status at baseline:** not measured **Bone status (osteoporosis, previous fractures? BMD?)** more than half of the participants had a previous fracture **Calcium intake monitoring?** - Not measured **Concomitant medication:** - not reported	*1) 1000 mg / day as calcium carbonate* *+* *800 IU / day of vitamin D3 (n = 1321)* *versus* *2) placebo (n = 1993)*	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Unclear, states “randomized” • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: ○ Intervention group: 33% ○ Control group: 1.6% • Described: no • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding, company provided study medication • **SELECTIVE REPORTING:** yes • **Other important methodological remarks** • Pilot study undertaken: patients of pilot study included for analysis (n=117) • Relatively low adherence in intervention group after 18 months: 58.6%
Prince 2006[44] Data on: mortality CHD	See studies from Bolland 2010			
Reid 2006[36] Data on: mortality MI	See studies from Bolland 2010			

Riggs 1998[40] Design: RCT Duration of follow-up: 4 years Data on : mortality	**<u>Inclusion criteria:</u>** - fully ambulatory - between 61 and 70 years of age - post-menopausal for 10 years or more **<u>Exclusion criteria:</u>** - history of renal lithiasis, impaired renal function, hypercalcemia, or hypercalciuria (>300 mg/24 h) - any disease known to affect bone or calcium metabolism - receiving oestrogen, large doses of vitamin D or calcium, or other drugs known to affect bone - a history of use of fluoride or bisphosphonate drugs	N = 236 **Mean age:** 66 years **Gender distribution:** 100% women **Vitamin D status at baseline:** serum 25(OH)D measured by the methods of Eisman et al. and Kumar et al. Mean for intervention 30.4 ±10.5 nm/ml mean for placebo: 29.7 ± 10.3 nm/ml **Bone status (osteoporosis, previous fractures? BMD?)** No subject had a history of osteoporotic fractures and all had normal BMD values **Dietary calcium intake monitoring?** Assessed by food questionnaire, -mean intervention group: 711± 276 mg / day - mean control group 717 ± 295 mg/day supplemental intake up to 500mg/day calcium acceptable **Concomitant medication:** women taking supplementary calcium at ≤500 mg/day and/or vitamin D at ≤800 IU/day at baseline were eligible for inclusion	*1600 mg/day Calcium (as calcium citrate) (n= 119)* *vs* *Placebo (n= 117)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Unclear • **BLINDING:** Adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and exclusions: 25 % • Described: yes • Balanced across groups: yes • **ITT:** no, PPA • **FUNDING**: no industry funding • **SELECTIVE REPORTING:** no • **Other important methodological remarks** : no power calculation shown • **Primary end point**: changes in bone mineral density

Salovaara (OSTPRE-FPS) 2007[64] Design: RCT No PL Duration: 3 years Data on: mortality	**<u>Inclusion criteria:</u>** - women aged 65 to 71 years - living in the northern savonia **<u>Exclusion criteria:</u>** taken part in any trials or BMD measurements of the OSTRPRE study	N = 3432 **Mean age:** 67 years **Gender distribution:** 100% women **Vitamin D status at baseline:** Measured by DiaSorin radioimmunoassay In a subsample of 350 women from each group Mean: 50 nmol/l **Bone status (osteoporosis, previous fractures? BMD?)** 35% had a previous fracture **Calcium intake monitoring?** Semi-quantitatively assessed by food frequency questionnaire Mean: 957 mg / day **Concomitant medication:** no data	*1000 mg of calcium as calcium carbonate* *+* *800 IU of cholecalciferol (n = 1586)* *versus* *no treatment (n = 1609)*	• **ALLOCATION CONCEALMENT**: Unclear • **RANDOMISATION:** Adequate • **BLINDING:** Assessors: unclear, others:adequate • **FOLLOW-UP:** • Lost-to follow-up, drop-out and Exclusions: 8,5% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: no industry funding, tablets donated by Nycomed • **SELECTIVE REPORTING:** no • **Primary end point:** risk of fractures • **Main finding:** non-significant decreased risk for fractures

Sambrook 2012[96] Study design: RCT MC No PL Duration 1 year Data on: Mortality CHD	**Inclusion criteria:** - aged >70 years - ambulant - considered likely to survive for more than 12 months **Exclusion criteria:** - taking vitamin D or calcium supplements - history of skin cancer in the last 3 years	N = 602 **Mean age:** 87 years **Gender distribution:** 58% female **Vitamin D status:** - mean: 33.5 nmol/l - measured by liquid chromatography tandem mass spectrometry **Bone status (osteoporosis, previous fractures? BMD?)** History of falls given, not fractures or BMD **Calcium intake monitoring?** No data **Concomitant medication?** No data	1) Increased sunlight exposure (n = 137) 2) Increased sunlight exposure plus calcium (n = 139) 3) control (no placebo) (n = 137)	• **ALLOCATION CONCEALMENT**: Adequate • **RANDOMISATION:** Adequate • **BLINDING:** Open label • **FOLLOW-UP:** • Lost-to follow-up, drop-out and exclusions: 23,8% • Described: yes • Balanced across groups: no • **ITT:** yes • **FUNDING**: neutral • **SELECTIVE REPORTING:** no • **Other important methodological remarks** : low adherence to intervention (median adherence:26%) • **Primary end point:** Improvement of vitamin D status and falls • **Main finding:** not effective

Table 65: characteristics of studies included in meta-analysis by Lewis et al. 2014

7.3 Summary and conclusions

One point is deduced of all grading since the results all come from post-hoc analyses.

Comparison: Calcium with or without vitamin D versus no calcium			
Bibliography: Bolland 2010 and Lewis 2014			
Outcomes	**N° of participants (studies) Follow up**	**Results**	**Quality of the evidence (GRADE)**
Myocardial infarction (Bolland)	10,210 (6)	RR = 1.27 (1.01-1.59) *Statistically significant*	⊕⊕⊖⊖LOW Study quality: -1, post-hoc analysis Consistency: -1, mixed interventions (with vit D or not), one study 50% on HRT (Lappe 2007), one study men only (Reid 2008) Directness: OK Imprecision: OK
Myocardial infarction (Lewis)	51,111 (7)	RR = 1.08 (0.93 – 1.25) *Statistically not significant*	⊕⊖⊖⊖ VERY LOW Study quality: -1, post-hoc analysis Consistency: -2, Jackson 2006 (WHI) accounts for a large number of patients (36,282), with around 50% on HRT or bisphosphonates. Is also a comparison of Ca+vit D vs other treatment and thus eclipses Ca vs placebo comparison due to its size Directness: OK Imprecision: OK
Stroke (Bolland)	10,584 (7)	RR = 1.12 (0.97 – 1.30) *Statistically not significant*	⊕⊕⊖⊖LOW Study quality: -1, post-hoc analysis Consistency: -1, mixed interventions (with vit D or not), one study 50% on HRT (Lappe 2007), one study all patients on alendronate (Bonnick 2007) Directness: OK Imprecision: OK

MI, stroke or sudden death **(Bolland)**	10,345 (7)	RR = 1.12 (0.97 – 1.30) *Statistically not significant*	⊕⊕⊖⊖LOW Study quality: -1, post-hoc analysis Consistency: -1, mixed interventions (with vit D or not), one study 50% on HRT (Lappe 2007), one study men only (Reid 2008) Directness: OK Imprecision: OK
All cause mortality / deaths **(Bolland)**	10,210 (6)	RR = 1.07 (0.95 – 1.19) *Statistically not significant*	⊕⊕⊖⊖LOW Study quality: -1, post-hoc analysis Consistency: -1, mixed interventions (with vit D or not), one study 50% on HRT (Lappe 2007), one study men only (Reid 2008) Directness: OK Imprecision: OK
All-cause mortality / deaths **(Lewis)**	62,383 (17)	RR = 0.96 (0.91 – 1.02) *Statistically not significant*	⊕⊖⊖⊖ VERY LOW Study quality: -1, post-hoc analysis Consistency: -2, Jackson 2006 (WHI) accounts for a large number of patients (36,282), with around 50% on HRT or bisphosphonates. Is also a comparison of Ca+vit D vs other treatment and thus eclipses Ca vs placebo comparison due to its size Directness: OK Imprecision: OK
CHD **(Lewis)**	48,460 (5)	RR = 1.02 (0.96 – 1.09) *Statistically not significant*	⊕⊖⊖⊖ VERY LOW Study quality: -1, post-hoc analysis Consistency: -2, Jackson 2006 (WHI) accounts for a large number of patients (36,282), with around 50% on HRT or bisphosphonates. Is also a comparison of Ca+vit D vs other treatment and thus eclipses Ca vs placebo comparison due to its size Directness: OK Imprecision: OK

Table 66: summary and conclusion for CV safety of calcium

We evaluated the effect of calcium supplementation with or without vitamin D on cardiovascular outcomes and mortality, and put two meta-analyses with differing conclusions side to side. Some important remarks must be made:

Both meta-analyses use studies that have included patients under HRT. Oestrogen is thought to have a protective cardiovascular effect but this remains under debate[102], [103]. This is especially important for the analyses done by Lewis et al. where the results from WHI trial are included. Since it is such a large trial, and accounts for a large number of patients in the analysis, it makes it difficult to form a firm conclusion.

Diverse population characteristics, inclusion and exclusion criteria are a recurrent problem in this review of literature for calcium and vitamin D interventions, however, some of the studies used by Bolland are highly similar in age, gender and population characteristics (e.g. Grant 2005, Prince 2006, Reid 2006). The literature group thinks that a re-analysis without the outlying studies (men only, population under HRT) might provide further information on a better defined population. Also, it is unfortunate that no analysis has analysed calcium-only interventions separately from calcium and vitamin D intervention.
In general, new studies with cardiovascular endpoints and mortality as primary outcomes are direly needed. The current research allows only to conclude to low or very low levels of evidence.

Summary:

It is unclear if treatment with calcium with or without vitamin D compared to no calcium significantly increases the risk of myocardial infarction.
Quality of evidence for a heightened risk: *VERY LOW to LOW*

Treatment with calcium with or without vitamin D compared to no calcium does not significantly increases the risk of stroke.
Quality of evidence: *LOW*

Treatment with calcium with or without vitamin D compared to no calcium does not significantly increases the risk of myocardial infarction, stroke or sudden death.
Quality of evidence: LOW

Treatment with calcium with or without vitamin D compared to no calcium does not significantly decrease the risk of death
Quality of evidence: VERY LOW to LOW

Treatment with calcium with or without vitamin D compared to no calcium does not significantly increases the risk of coronary heart disease.
Quality of evidence: LOW

APPENDIX: Search strategy

The following search strategy was used in Pubmed and Medline databases. This search strategy contains terms regarding the safety of vitamin D and general mortality, but articles pertaining to this topic were, after discussion with the organising committee, not withheld.

(((
((vitamin D[MeSH Terms] OR cholecalciferol[Title/Abstract] OR "vit D"[Title/Abstract] OR "vit D3"[Title/Abstract] OR "vitamin D"[Title/Abstract] OR "vitamin D3"[Title/Abstract] OR colecalciferol[Title/Abstract])
AND
("Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR osteoporo*[Title/Abstract] OR bone*[Title/Abstract] OR skelet*[Title/Abstract] OR osteopath*[Title/Abstract] OR osteomalac*[Title/Abstract] OR fracture*[Title/Abstract])
AND
("2012/10/01"[Date - Publication] : "2014/11/30"[Date - Publication]))

OR

((vitamin D[MeSH Terms] OR cholecalciferol[Title/Abstract] OR "vit D"[Title/Abstract] OR "vit D3"[Title/Abstract] OR "vitamin D"[Title/Abstract] OR "vitamin D3"[Title/Abstract] OR colecalciferol[Title/Abstract])
AND
("Accidental Falls"[Mesh] OR falls[Title/Abstract] OR "fall risk"[Title/Abstract] OR fall[Title/Abstract] OR falling[Title/Abstract] OR fallen*[Title/Abstract] OR slip*[Title/Abstract])
AND
("aged, 80 and over"[MeSH Terms] OR "aged"[MeSH Terms] OR old[Title/Abstract] OR older*[Title/Abstract] OR senior*[Title/Abstract] OR elder* OR geriatric*[Title/Abstract])
AND
("2012/02/01"[Date - Publication] : "2014/11/30"[Date - Publication]))

OR

((vitamin D[MeSH Terms] OR cholecalciferol[Title/Abstract] OR "vit D"[Title/Abstract] OR "vit D3"[Title/Abstract] OR "vitamin D"[Title/Abstract] OR "vitamin D3"[Title/Abstract] OR colecalciferol[Title/Abstract])
AND
("Mortality"[Mesh] OR mortality[Title/Abstract] OR “fatal outcome”[Title/Abstract] OR death[Title/Abstract] OR survival[Title/Abstract])
AND
("2012/01/01"[Date - Publication] : "2014/11/30"[Date - Publication]))

OR

((calcium[MeSH Terms] OR calcium compounds[MeSH Terms] OR (calcium*[Title/Abstract] NOT (calcium channel[Title/Abstract] OR calcium antagonists[Title/Abstract])))
AND
("Osteoporosis"[Mesh] OR "Fractures, Bone"[Mesh] OR osteoporo*[Title/Abstract] OR bone*[Title/Abstract] OR skelet*[Title/Abstract] OR osteopath*[Title/Abstract] OR osteomalac*[Title/Abstract] OR fracture*[Title/Abstract])
AND
("2006/12/01"[Date - Publication] : "2014/11/30"[Date - Publication]))

OR

((calcium[MeSH Terms] OR calcium compounds[MeSH Terms] OR (calcium*[Title/Abstract] NOT (calcium channel[Title/Abstract] OR calcium antagonists[Title/Abstract])))
AND
(cardiovascular [tiab] OR MI [tiab] OR myocardial infarct* [tiab] OR stroke [tiab] OR sudden death [tiab] OR "Myocardial Infarction"[Mesh] OR "Stroke"[Mesh] OR "Death, Sudden"[Mesh] OR "Mortality"[Mesh] OR mortality[Title/Abstract] OR “fatal outcome”[Title/Abstract] OR death[Title/Abstract] OR survival[Title/Abstract])
AND
("2013/04/24"[Date - Publication] : "2014/11/30"[Date - Publication]))

)

AND

(randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR placebo[tiab] OR systematic[sb] OR medline[TIAB])) NOT ((animals[MeSH Terms] NOT human[MeSH Terms]) OR pregnant woman[MeSH Terms] OR "Child"[Mesh] OR "Infant"[Mesh] OR "Adolescent"[Mesh])) NOT ("Tooth Calcification"[Mesh] OR "Tooth Components"[Mesh] OR "Tooth"[Mesh] OR Tooth [Title] OR "Renal Insufficiency"[Mesh] OR "Renal Dialysis"[Mesh])x[Title] OR "Renal Insufficiency"[Mesh] OR "Renal Dialysis"[Mesh])

References

1 Brouwers, M.C. et al., 2010. AGREE II: Advancing guideline development, reporting and evaluation in health care. *Journal of Clinical Epidemiology*, 63(12), pp.1308–1311.

2 Avenell, A., Mak, J.C.S. & O'Connell, D., 2014. Vitamin D and vitamin D analogues for preventing fractures in post-menopausal women and older men. *The Cochrane database of systematic reviews*, 4, p.CD000227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24729336.

3 Gillespie, L.D. et al., 2012. Interventions for preventing falls in older people living in the community. *The Cochrane database of systematic reviews*, 9, p.CD007146. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22972103

4 Cameron, I.D. et al., 2010. Interventions for preventing falls in older people in nursing care facilities and hospitals. *The Cochrane database of systematic reviews*, (1), p.CD005465.

5 Tang, B.M.P. et al., 2007. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. *Lancet*, 370(9588), pp.657–66. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17720017

6 Bischoff-Ferrari, H.A. et al., 2007. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *The American journal of clinical nutrition*, 86(6), pp.1780–1790.

7 Bolland, M.J. et al., 2010. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ (Clinical research ed.)*, 341, p.c3691.

8 Lewis, J.R. et al., 2014. The Effects of Calcium Supplementation on Verified Coronary Heart Disease Hospitalization and Death in Postmenopausal Women: A Collaborative Meta-Analysis of Randomized Controlled Trials. *Journal of Bone and Mineral Research*, p.n/a–n/a. Available at: http://doi.wiley.com/10.1002/jbmr.2311.

9 Atkins, D. et al., 2004. Grading quality of evidence and strength of recommendations. *BMJ (Clinical research ed.)*, 328(7454), p.1490.

10 GRADE working group. Available from: www.gradeworkinggroup.org.

11 Guyatt, G.H. et al., 2008. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ (Clinical research ed.)*, 336(7650), pp.924–6.

12 Belgisch Centrum voor Farmaceutische Informatie, "Geneesmiddelen en risico van vallen" Available online <http://www.bcfi.be/Folia/2003/F30N09E.cfm>, accessed on 26/02/2015

13 Pols P., Wittenberg J. "CBO-Richtlijn 'Osteoporose' tweede herziening" 2002 *Nederlands Tijdschrift Voor Geneeskunde.* Available online <https://www.ntvg.nl/artikelen/cbo-richtlijn-osteoporose-tweede-herziening/ingezonden-mededelingen>

14 Baeyens, H. & Desmet, P., 2011. Vitamine D-substitutie bij ouderen in woon- en zorgcentra : mission impossible of haalbare uitdaging ? *Tijdschr. voor Geneeskunde*, 67(00), pp.1–7.

15 Committee for Medicinal Products for Human use (CMPH), "Guideline on the evaluation of medicinal products in the treatment of primary osteoporosis". 2007. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003405.pdf - last consulted on 10.02.2015

16 Van Mierlo, L.A.J. et al., 2006. Blood pressure response to calcium supplementation: a meta-analysis of randomized controlled trials. *Journal of human hypertension*, 20(8), pp.571–80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16673011

17 Dickinson, H.O. et al., 2006. Calcium supplementation for the management of primary hypertension in adults. *The Cochrane database of systematic reviews*, (2), p.CD004639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16625609

18 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. *BMJ (Clinical research ed.)*, 348, p.g2035.

19 Bjelakovic, G. & Gluud, L., 2014. Vitamin D supplementation for prevention of mortality in adults. *Cochrane Database Syst Rev*, (1).

20 CBO. Richtlijn osteoporose en fractuurpreventie. derde herziening. 2011.

21 Florence R AS, Benedict L, Compo R, Jensen A, Kalogeropoulou D, Kearns A, Larson S, Mallen E, O'Day, K PA, Webb B. Diagnosis and Treatment of Osteoporosis. Updated July 2013. Institute for Clinical Systems Improvement 2013.

22 LeFevre, M.L., 2015. Screening for Vitamin D Deficiency in Adults: U.S. Preventive Services Task Force Recommendation Statement. *Annals of Internal Medicine*, 162(2), p.133. Available at: http://annals.org/article.aspx?doi=10.7326/M14-2450.

23 Moyer, V.A., 2013. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. *Annals of internal medicine*, 158(9), pp.691–6. Available at: http://annals.org/article.aspx?articleid=1655858 [Accessed February 18, 2015].

24 National Institure For Health and Care Excellence. Assessment and prevention of falls in older people. Clinical

References

guidance CG 161. 2013.

25 Rosen, C.J. et al., 2012. IOM committee members respond to endocrine society vitamin D guideline. *Journal of Clinical Endocrinology and Metabolism*, 97(4), pp.1146–1152.

26 Health Council of the Netherlands. Evaluatie van de voedingsnormen voor vitamine D. 2012.

27 IOM (Institute of Medicine). Dietary Reference Intakes for Calcium and Vitamin D. 2011.

28 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. *Journal of Clinical Endocrinology and Metabolism*, 92(4), pp.1415–1423.

29 Avenell, A. et al., 2009. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. *The Cochrane database of systematic reviews*, (2), p.CD000227.

30 Abrahamsen, B., 2010. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. *BMJ (Clinical research ed.)*, 340, p.b5463.

31 Bischoff-Ferrari, H.A. et al., 2005. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. *JAMA,* 293(18), pp.2257–2264.

32 Jackson, R.D. et al., 2006. Calcium plus vitamin D supplementation and the risk of fractures. *The New England journal of medicine*, 354(7), pp.669–83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16481635

33 Bischoff-Ferrari, H.A. et al., 2009. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. *BMJ (Clinical research ed.)*, 339, p.b3692.

34 Heaney, R.P. et al., 2012. A review of calcium supplements and cardiovascular disease risk. *Advances in nutrition (Bethesda, Md.)*, 3(6), pp.763–71.

35 Radford, L.T. et al., 2014. The Auckland calcium study: 5-year post-trial follow-up. *Osteoporosis international*, 25(1), pp.297–304. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24114400

36 Reid, I.R. et al., 2006. Randomized Controlled Trial of Calcium in Healthy Older Women. *American Journal of Medicine*, 119(9), pp.777–785.

37 Reid, I.R. et al., 1993. Effect of calcium supplementation on bone loss in postmenopausal women. *The New England journal of medicine*, 328(7), pp.460–464.

38 Chevalley, T. et al., 1994. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporosis international*, 4(5), pp.245–252.

39 Recker, R.R. et al., 1996. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. *Journal of bone and mineral research,* 11(12), pp.1961–1966.

40 Riggs, B.L. et al., 1998. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. *Journal of bone and mineral research*, 13(2), pp.168–174.

41 Peacock, M. et al., 2000. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. *Journal of Clinical Endocrinology and Metabolism*, 85(9), pp.3011–3019.

42 Fujita, T. et al., 2004. Reappraisal of Katsuragi Calcium study, a prospective, double-blind, placebo-controlled study of the effect of active absorbable algal calcium (AAA Ca) on vertebral deformity and fracture. *Journal of Bone and Mineral Metabolism*, 22(1), pp.32–38.

43 Grant, A.M., 2005. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium or vitamin D, RECORD): A randomised placebo-controlled trial. *Lancet*, 365(9471), pp.1621–1628.

44 Prince, R.L. et al., 2006. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. *Archives of internal medicine*, 166(8), pp.869–875.

45 Reid, I.R. et al., 1995. Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial. *The American journal of medicine*, 98(4), pp.331–335.

46 Bischoff-Ferrari, H.A. et al., 2008. Effect of calcium supplementation on fracture risk: a double-blind randomized controlled trial. *The American journal of clinical nutrition*, 87(6), pp.1945–1951.

47 Avenell, A. et al., 2004. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. *Clinical trials (London, England)*, 1(6), pp.490–498.

48 Glendenning, P., 2012. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research*, 27(1), pp.170–6. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21956713

49 Harwood, R.H. et al., 2004. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NoNOF) study. *Age and Ageing*, 33(1), pp.45–51.

References

50 Law, M. et al., 2006. Vitamin D supplementation and the prevention of fractures and falls: Results of a randomised trial in elderly people in residential accommodation. *Age and Ageing*, 35(5), pp.482–486.

51 Lips, P. et al., 1996. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Annals of internal medicine*, 124(16), pp.400–406.

52 Lyons, R. a. et al., 2007. Preventing fractures among older people living in institutional care: A pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. *Osteoporosis International*, 18(6), pp.811–818.

53 Meyer, H.E. et al., 2002. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. *Journal of bone and mineral research,* 17(4), pp.709–715.

54 Mitri, J. et al., 2011. Effects of vitamin D and calcium supplementation on pancreatic b cell function , insulin sensitivity , and glycemia in adults at high risk of diabetes : the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial 1 – 4. *Am J Clin Nutr*, 94(4), pp.486–494.

55 Smith, H. et al., 2007. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. *Rheumatology (Oxford, England)*, 46(April), pp.1852–1857.

56 Trivedi, D.P., Doll, R. & Khaw, K.T., 2003. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ (Clinical research ed.)*, 326(7387), p.469.

57 Sanders, K.M. et al., 2010. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. *JAMA : the journal of the American Medical Association*, 303(18), pp.1815–1822.

58 Witham, M.D. et al., 2010. The effects of vitamin D supplementation on physical function and quality of life in older patients with heart failure a randomized controlled trial. *Circulation: Heart Failure*, 3(2), pp.195–201.

59 Witham, M.D. et al., 2013. Cholecalciferol treatment to reduce blood pressure in older patients with isolated systolic hypertension the VitDISH randomized controlled trial. *JAMA Internal Medicine*, 173(18), pp.1672–1679.

60 Lopez-Torres Hidalgo, J., 2011. Prevention of falls and fractures in old people by administration of calcium and vitamin D, randomized clinical trial. *BMC public health*, 11, p.910.

61 Chapuy, M.C. et al., 1992. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *The New England journal of medicine*, 327(23), pp.1637–1642.

62 Chapuy, M.C. et al., 2002. Combined calcium and vitamin D3 supplementation in elderly women: Confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: The decalyos II study. *Osteoporosis International*, 13(3), pp.257–264.

63 Dawson-Hughes, B. et al., 1997. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *The New England journal of medicine*, 337(10), pp.670–676.

64 Salovaara, K. et al., 2010. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial--the OSTPRE-FPS. *Journal of bone and mineral research* , 25(7), pp.1487–1495.

65 Porthouse, J. et al., 2005. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. *BMJ (Clinical research ed.)*, 330(7498), p.1003.

66 Bolton-Smith, C. et al., 2007. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. *Journal of bone and mineral research,* 22(4), pp.509–519.

67 Bischoff, H. a et al., 2003. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *Journal of bone and mineral research*, 18(2), pp.343–351.

68 Burleigh, E., McColl, J. & Potter, J., 2007. Does vitamin D stop inpatients falling? A randomised controlled trial. *Age and ageing*, 36(5), pp.507–513.

69 Garay Lillo, J. et al., 1997. Géminis: Estudio prospectivo, multicéntrico y aleatori para valorar el efecto del Fosfato Tricálcico versus Fosfato Tricálcico + 25(OH) Vitamina D sobre el riesgo de fracturas en mujerioes ancianas. *Geriátrika*, 13(6), pp.24–28.

70 Janssen, H.C.J.P., Samson, M.M. & Verhaar, H.J.J., 2010. Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation. *Aging clinical and experimental research*, 22(1), pp.78–84.

71 Pfeifer, M. et al., 2000. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *Journal of bone and mineral research,* 15(6), pp.1113–1118.

72 Komulainen, M.H. et al., 1998. HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; A 5 year randomized trial. *Maturitas*, 31(1), pp.45–54.

73 Flicker, L. et al., 2005. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. *Journal of the American Geriatrics Society*, 53(11), pp.1881–1888.

References

74 Pfeifer, M. et al., 2009. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. *Osteoporosis international*, 20(2), pp.315–322.

75 Prince, R.L. et al., 2008. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Archives of internal medicine*, 168(1), pp.103–108.

76 Karkkainen, M. et al., 2010. Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71 years: a 3-year randomized population-based trial (OSTPRE-FPS). *Osteoporosis international* , 21(12), pp.2047–2055.

77 Graafmans, W.C. et al., 1996. Falls in the elderly: a prospective study of risk factors and risk profiles. *American journal of epidemiology*, 143(11), pp.1129–36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8633602

78 Lips, P. et al., 1996. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. *Annals of internal medicine*, 124(16), pp.400–406.

79 Broe, K.E. et al., 2007. A higher dose of vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. *Journal of the American Geriatrics Society*, 55(2), pp.234–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17302660

80 Lopez-Torres Hidalgo, J., 2011. Prevention of falls and fractures in old people by administration of calcium and vitamin D, randomized clinical trial. *BMC public health*, 11, p.910.

81 Bischoff-Ferrari, H. a, Orav, E.J. & Dawson-Hughes, B., 2006. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Archives of internal medicine*, 166(4), pp.424–430.

82 Latham, N.K. et al., 2003. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: The frailty interventions trial in elderly subjects (FITNESS). *Journal of the American Geriatrics Society*, 51(3), pp.291–299.

83 Bischoff-Ferrari, H.A. et al., 2010. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Archives of internal medicine*, 170(9), pp.813–820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458090.

84 Bischoff-Ferrari, H.A. et al., 2010. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. *Archives of internal medicine*, 170(9), pp.813–820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20458090.

85 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. *Journal of the American Geriatrics Society*, 63(2), pp.211–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25641225 [Accessed February 15, 2015].

86 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. *Journal of the American Geriatrics Society*, 63(2), pp.211–21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25641225 [Accessed February 15, 2015].

87 Murad, M.H. et al., 2011. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. *The Journal of clinical endocrinology and metabolism*, 96(10), pp.2997–3006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21795448 [Accessed March 2, 2015].

88 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. *Archives of internal medicine*, 169(6), pp.551–561.

89 Bolland, M.J., Grey, A. & Reid, I.R., 2014. Differences in overlapping meta-analyses of vitamin D supplements and falls. *The Journal of clinical endocrinology and metabolism*, 99(11), pp.4265–72. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25093621 [Accessed March 17, 2015].

90 Arden, N.K. et al., 2006. Knee pain, knee osteoarthritis, and the risk of fracture. *Arthritis and rheumatism*, 55(4), pp.610–5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16874784 [Accessed March 4, 2015].

91 Reid, I.R. et al., 2011. Cardiovascular effects of calcium supplementation. *Osteoporosis international*, 22(6), pp.1649–1658.

92 Baron, J.A. et al., 1999. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *The New England journal of medicine*, 340(2), pp.101–107.

93 Lappe, J.M. et al., 2007. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. *The American journal of clinical nutrition*, 85(6), pp.1586–1591.

94 Reid, I.R. et al., 2008. Randomized controlled trial of calcium supplementation in healthy, nonosteoporotic, older men. *Archives of internal medicine*, 168(20), pp.2276–2282.

95 Larsen, E.R., Mosekilde, L. & Foldspang, A., 2004. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. *Journal of bone and mineral research* , 19(3), pp.370–378.

96 Sambrook, P.N., 2012. Does increased sunlight exposure work as a strategy to improve vitamin D status in the

References

elderly: a cluster randomised controlled trial. *Osteoporosis international*, 23(2), pp.615–24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21369788

97 Bonnick, S. et al., 2007. Treatment with alendronate plus calcium, alendronate alone, or calcium alone for postmenopausal low bone mineral density. *Current medical research and opinion*, 23(6), pp.1341–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17594775

98 Brazier, M. et al., 2005. Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: Results of a multicenter, randomized, double-blind, placebo-controlled study. *Clinical Therapeutics*, 27(12), pp.1885–1893.

99 Baeksgaard, L., Andersen, K.P. & Hyldstrup, L., 1998. Calcium and Vitamin D Supplementation Increases Spinal BMD in Healthy, Postmenopausal Women. *Osteoporosis International*, 8(3), pp.255–260.

100 Chailurkit, L. et al., 2010. Discrepant influence of vitamin D status on parathyroid hormone and bone mass after two years of calcium supplementation. *Clinical endocrinology*, 73(2), pp.167–172.

101 Krieg, M. a et al., 1999. Effect of supplementation with vitamin D3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study. *Osteoporosis international*, 9, pp.483–488.

102 Valdiviezo, C., Lawson, S. & Ouyang, P., 2013. An update on menopausal hormone replacement therapy in women and cardiovascular disease. *Current opinion in endocrinology, diabetes, and obesity*, 20(2), pp.148–55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23422240

103 Boardman, H.M. et al., 2015. Hormone therapy for preventing cardiovascular disease in post-menopausal women. *The Cochrane database of systematic reviews*, 3, p.CD002229. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25754617