

The impact of vitamin D supplementation on fractures, falls and mortality: an umbrella review of systematic reviews and meta-analyses of randomized controlled trials  
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### Citation

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### Review question

What is the effect of vitamin D supplementation on falls, fractures and/or mortality in adults and elderly? The aim of this umbrella review is to evaluate the effect of vitamin D supplementation in adults and elderly, on the risk of falls, fractures and mortality, based on published systematic reviews of Randomized Controlled Trials (RCTs). It will apply a quality assessment instrument that will help stratify evidence gathered and findings in previous meta-analyses.

### Searches

We searched MEDLINE, PubMed, and Embase and Cochrane databases using relevant MeSHs and key words, from January 1, 2010 till 13 July 2018, in order to cover the reviews published following vitamin D guidelines issued by 2 major societies, the Institute of Medicine in 2009 [1], and the Endocrine Society in 2011[2]. The terms used in the search strategy included: Vitamin D; falls, fractures, mortality, randomized controlled trials, meta-analyses, systematic review. See Appendix 1 for search strategy details. We will search epistemonikos, which is a database for the best evidence based health care (<https://www.epistemonikos.org/>). We will manually review the citations of included systematic reviews and narrative reviews on the topic. We will search Google Scholar for potential systematic reviews that we may have missed. We will contact vitamin D experts for queries about ongoing or unpublished reviews on the topic.

### Types of study to be included

We will include systematic reviews of randomized controlled trials, given that they represent the highest quality of evidence

#### Inclusion criteria

- o Systematic reviews (SR) or meta-analyses (MAs) of RCTs
- o English and non-English papers

#### Exclusion criteria

- o Narrative reviews
- o Systematic Reviews of nonrandomized studies
- o Systematic Reviews published as abstracts only

### Condition or domain being studied

There is considerable variation in the recommended vitamin D target level and maintenance dosing for the general healthy adult across different society guidelines (Ross 2010; Holick 2011; Pludowski 2013; Rizzoli 2013). Desirable vitamin D levels range from 25 to 75 nmol/L (10 to 30 ng/ml), according to various societies.

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To define the appropriate serum vitamin D level, both the Institute of Medicine (IOM) and the Endocrine Society (ES) reviewed the same evidence for skeletal health indicators, however, both their analysis and recommendations differ (El hajj Fuleihan 2015). The IOM supports a level of 20 ng/ml (Ross 2010), while the ES recommends at least 30 ng/ml (Holick 2011). Likewise, the recommended maintenance vitamin D dose for healthy adults also differ even when aiming for the same target (Ross 2010; NICE 2018; Hanley 2010). The IOM recommend a dose of 600 IU/d for ages 19 to 70 years and 800 IU/d for elderly aged >70 years (Ross 2010; Lötscher 2012). Lower dosing, 400 IU/d, is recommended by both the National Osteoporosis Society (NOS) 2017 and the National Institute for Health and Clinical Excellence (NICE) 2018 guidelines, while higher dosing of 1, 500-2, 000 IU/d is recommended by the ES guidelines (Holick 2011).

### Participants/population

Inclusion:

- SR including trials conducted on:
  - o Adults (> 18 years of age)
  - o Both men and women
  - o Community dwelling and institutionalized

Exclusion:

- SR including trials conducted in
  - o Pregnant and lactating women
  - o Individuals with advanced chronic illness (chronic kidney disease (GFR < 30ml/min), chronic advanced liver disease, heart failure (NYHA class >3), Crohn's disease, HIV, and cancer in more than 25% of the population)
  - o Individuals with conditions or on drug therapy that might affect vitamin D metabolism or vitamin D binding protein/metabolism (anticonvulsants, steroids, anti fungal, malabsorption, bypass surgery) in more than 25% of the population

### Intervention(s), exposure(s)

Inclusion:

- o SR where the intervention is Vitamin D supplementation, with or without calcium, regardless of the supplementation form, or frequency or duration.

Exclusion:

- o SR where the intervention of interest is active or synthetic vitamin D in more than 25% of the trials.
- o SR where the intervention of interest where vitamin D is administered as single high oral dose (Stoss therapy) in more than 25 % of trials

### Comparator(s)/control

Inclusion:

- o SR where placebo/control or a different vitamin D supplementation dose is the comparator

Exclusion:

- o SR where the co-intervention differs between arms in more than 25% of the trials

### Context

There has been a rapid increase in vitamin D research in the past several years with a resultant upsurge in systematic reviews and meta-analyses synthesis. Clinical trials account for approximately 8% of the published research, more than half of which were published in the past 10 years

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(www.ncbi.nlm.nih.gov/PubMed). Lately, several meta-analyses on vitamin D supplementation yielded conflicting findings, questioning the benefits of vitamin D supplementation in general and on musculo-skeletal health and mortality in specific (Bolland 2018; Avenell 2016; Weaver 2016; Cameron 2018; Zhao 2017; Guirguis-Blake 2018; Guo 2013; Tricco 2017; Wu 2017). For instance, a trial sequential meta-analysis concluded that vitamin D supplementation does not prevent falls or fractures in community dwelling and institutionalized individuals, and there was no difference in effect comparing higher to lower doses (Bolland 2018). In another review, vitamin D supplementation, compared to control reduced the number of falls by 28% in institutionalized individuals (Cameron 2018). The USPTF review on vitamin D supplementation in the community concluded that vitamin D alone or with concomitant calcium does not reduce the risk of falls (Guirguis-Blake 2018). Similarly, data on mortality varies widely. Some meta-analyses reported reduction in mortality (Zheng 2013; Chowdry 2014), while others did not (Bolland 2014). This variability in findings is related to population characteristics, intervention regimen, definition and assessment of outcomes, quality of studies and risk of bias, and others

### Main outcome(s)

Outcomes will be collected as reported in the individual systematic reviews:

1. Relative risk of the number of falls or the number of patients suffering from one or more falls (number of fallers, repeated fallers, and the number of falls, per treatment arm)
2. Relative risk of hip fracture
3. Relative risk of any fracture, or fracture at specific sites: spine, forearm, hip, humerus
3. Relative risk of mortality

### Timing and effect measures

Any time, depending on individual systematic reviews

### Additional outcome(s)

Adverse events  
Compliance

### Timing and effect measures

Any time, depending on individual systematic reviews

### Data extraction (selection and coding)

We will review the title and abstract of retrieved citations in duplicate and independently, using title and abstract screening guide. We will perform a calibration exercise, until discrepancy between reviewers falls below 10%. The citation included by at least one of the reviewers will be considered as eligible.

We will retrieve the full text of these potentially eligible systematic reviews and two reviewers will assess them in duplicate and independently for eligibility, using a standardized and pilot tested full text screening forms. The reason for excluding systematic reviews after full text screening will be recorded. Neither of the review authors will be blind to the journal titles or to the study authors or institutions. In case of discrepancy, a co-author, content or methodology expert will be consulted as indicated. Using standardized and pilot tested forms, two reviewers will extract data independently and in duplicate from each eligible systematic review. To ensure consistency across reviewers, we will conduct calibration exercises of data abstraction.

We will assess the quality of included SRs using the critical appraisal tool AMSTAR 2

### Risk of bias (quality) assessment

Two review authors (MC, GEHF) will assess the quality of the systematic reviews, in duplicate and independently, using the critical appraisal tool AMSTAR 2 [39]. AMSTAR 2 enables the appraisal of systematic reviews of both randomized and non-randomized healthcare intervention studies [39]. It includes 16 domains with 7 of them being considered as critical [39]. It allows an overall rating based on weaknesses in critical domains but is not intended to generate an overall score. The critical domains include the following: protocol registration before initiation of the review, adequacy of the literature search, justification for excluding individual studies, appropriateness of meta-analytical methods in addition to the risk of bias from individual studies being included in the review, consideration of risk of bias when interpreting the results of

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the review and assessment of the presence and likely impact of publication bias.

For the risk of bias assessment in the individual trials, we will describe the assessment as provided in each systematic review.

We will investigate potential reasons for different effect estimates across MAs, as investigated previously by Akl et al (in press)

### Strategy for data synthesis

The aim of an Umbrella review is to present an overall summary of findings for a particular question and not any further “synthesis” of the results of these publications (Aromatis 2015). The results of all included studies will be presented to the reader as an accurate, verbatim replication of the synthesized findings from the source review, to allow readily available and easily interpretable overview of the findings. Tabular presentation of findings will be used where overall effect estimates extracted from systematic reviews or what other similar numerical data are presented. Where quantitative data is presented, the number of studies that inform the outcome and number of participants (from included studies) and the heterogeneity of the results of included reviews will also be reported. Clear indication of overlap of original research studies in each of the included research syntheses will be presented. We will also assess evidence of publication bias (Aromatis 2015)

### Analysis of subgroups or subsets

Not applicable

### Contact details for further information

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### Type and method of review

Intervention, Narrative synthesis, Systematic review

### Anticipated or actual start date

02 September 2018

### Anticipated completion date

01 January 2020

### Funding sources/sponsors

None

### Conflicts of interest

### Language

English

### Country

Lebanon

### Stage of review

Review Ongoing

### Subject index terms status

Subject indexing assigned by CRD

### Subject index terms

Accidental Falls; Dietary Supplements; Fractures, Bone; Humans; Nutrition Therapy; Randomized Controlled Trials as Topic; Vitamin D

### Date of registration in PROSPERO

24 April 2019

### Date of publication of this version

24 April 2019

### Details of any existing review of the same topic by the same authors

### Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

### Versions

24 April 2019

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This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. The registrant confirms that the information supplied for this submission is accurate and complete. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.