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Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

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3 **Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in**
4 **children and adolescents: A systematic review and meta-analysis protocol**
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Abstract

Introduction: The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal functions has long been documented. However, review investigations on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents are scarce. The aim of current study was to assess the impact of various doses of vitamin D supplementation on serum 25-hydroxyvitamin D concentrations in children and adolescents, and to identify relevant determinants of variations in the effect of vitamin D supplementation.

Methods: PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases to the 27-Sep-2017 will systematically be searched for randomized controlled trials of vitamin D supplementation compared with placebo, no intervention control, or comparative arm investigations. One reviewer will assess articles for eligibility according to prespecified selection criteria, after which data extraction and quality appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed using Jadad scales. Meta-analyses will be conducted where appropriate. We will express continuous measures (i.e serum 25-hydroxyvitamin D concentration) as mean differences (MDs) with 95% CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and using Chi² test on N-1 degrees of freedom, with a significance level of $\alpha=0.1$. We will also assess the individual study and subgroup characteristics and perform a sensitivity analysis. Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

Ethics and dissemination: Ethics approval is not required because the work is carried out on published documents. The authors will publish findings from this review through peer-reviewed publication or conference presentations.

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Trial registration number: PROSPERO CRD42017067179.

Keywords: Vitamin D; 25-hydroxyvitamin D; children; adolescents; meta-analysis

For peer review only

Strengths and limitations of this study

- This systematic review will comprehensively assess the effectiveness and safety of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations.
- The study screening, data extraction and quality assessment will be fulfilled by two independent reviewers.
- Some variables including sex, 25-hydroxy vitamin D baseline level, length of intervention, frequency of intervention, doses of vitamin D supplementation may cause considerable heterogeneity in this review.
- Studies may not systematically report all outcomes.
- The systematic review will include only published data.

Introduction

The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal functions has long been clarified. Currently, vitamin D deficiency is a global problem, and a recent systematic review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-hydroxyvitamin D [1]. Since childhood and adolescence life cycles increase vitamin requirements for the growth of muscle and bone, vitamin D deficiency is also significantly observed during this period. Low vitamin D status has recently been reported in children and adolescents across countries of the Middle East such as Iran [2, 3], Saudi Arabia [4], Jordan [5], and United Arab Emirates [6], as well as in South East Asia [7, 8], Europe [9], and the United States [10]. Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made for evaluating the influence of variable doses of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents [11], a factor crucial for stipulating dietary recommendations. Based on recommendations of the Institute of Medicine (IOM) in 2011, the recommended dietary allowance (RDA) is 600 IU for 9-18-year old children and adolescents [12], whereas based on recommendations of the Endocrine Society, 9-18-year old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000 IU of vitamin D is essential to maintain levels of 25-hydroxyvitamin D > 30 ng/ml [13]; this controversy may be explained by the fact that IOM recommendations are based on achieving the target level of ≥ 20 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on achieving ≥ 30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for adolescents at risk of vitamin D deficiency such as obesity [14], emphasizing the differences in recommendations of these two scientific societies.

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3 Serum level of 25-hydroxyvitamin D is a commonly used marker of the long-term vitamin D
4 nutritional status of individuals. Exposure to sunlight is the most important factor in the synthesis
5 of vitamin D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based
6 on the cultural beliefs of individuals. Supplementation of vitamin D and dietary intake of limited
7 foods also increase 25-hydroxyvitamin D concentrations. Previous studies in adults showed that
8 baseline 25-hydroxyvitamin D, concurrent calcium intakes, and the level of overweight and
9 obesity are among other factors which may affect 25-hydroxyvitamin D in response to vitamin D
10 supplementation [15]. Studies have shown a direct association of increase in body mass index
11 (BMI) with decrease in both 25-hydroxyvitamin D and 1,25-hydroxyvitamin D and increase in
12 parathyroid hormone [16-18]. A stronger correlation between the fat mass and concentration of
13 25-hydroxyvitamin D has also been reported due to reduction in calcium and vitamin D intake,
14 bioavailability and subcutaneous synthesis of vitamin D, and activation of 25-hydroxyvitamin D,
15 increase in vitamin D catabolism or 25-hydroxy vitamin D sequestration in fat tissue [19, 20]. A
16 systematic review in adults found that the average increase in serum 25-hydroxyvitamin D
17 concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [21]. Recently a review study
18 from the Middle East and North Africa (MENA) region showed that intakes of intermediate
19 vitamin D dose of 1000–2000 IU daily may be necessary to facilitate for achievement of optimal
20 25-hydroxyvitamin D level of 20 ng/ml in children and adolescents [11].
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45 To the best of our knowledge, to date, no systematic review has been conducted on the effect of
46 vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and adolescents
47 worldwide. In previous original studies also the optimum level of 25-hydroxyvitamin D had not
48 been determined [22-24], and because of lower power, the graded response to vitamin D
49 supplementation could not be explored. This review will therefore aim at determining the
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effectiveness of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations and assessing the graded response to vitamin D supplementation.

Methods

Objectives

- To assess the effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents.
- To determine the effectiveness of variable doses of vitamin D supplementation in children and adolescents for improving serum 25-hydroxyvitamin D concentrations.
- To determine if the effect of vitamin D supplementation on serum 25-hydroxyvitamin D varies by baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.

Types of studies

We will include randomized controlled trials of vitamin D supplementation compared with placebo, no intervention control, or comparative arm studies, which examine the response to different doses of vitamin D supplementation (with or without a placebo arm), irrespective of their endpoint of interest, but they must have reported 25-hydroxyvitamin D level at baseline and at the end of the study.

Types of participants

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3 Healthy children and adolescents (aged ≤ 18 years old) given vitamin D as a preventive measure
4 of certain diseases or individuals with mild diseases that have no reason to have altered vitamin
5 D metabolism.
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10 Exclusion criteria:

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13 a) Rickets in children characterized by low 25(OH)D, below 15 ng/ml with radiologic or
14 laboratory evidence requires higher doses of vitamin D supplementation (higher than those
15 recommended for the general population).
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21 b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or
22 below 30 ml/min), liver disease, heart failure (NYHA class 3 or more)
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27 c) Individuals with conditions or on drug therapy that might affect vitamin D metabolism and
28 vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption,
29 bypass surgery)
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34 *Types of intervention*

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37 Inclusion criteria:

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40 Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with
41 or without calcium supplementation
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45 Exclusion criteria:

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48 a) Studies that used active vitamin D supplementation as this type of supplementation is not
49 recommended for the general population.
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54 b) Studies that used vitamin D supplementation given intra muscularly
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3 c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin
4 cannot be defined accurately
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8 **Search methods for identification of studies**

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10 **Electronic searches**

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14 We will perform a systematic search of published randomized trials on vitamin D intervention in
15 subjects aged ≤ 18 years old in PubMed, Scopus, ISI Web of Science, and Cochrane Central
16 Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017 using eligible keywords
17 in titles or abstracts (for details on search strategies see Supplementary File 1), using the
18 following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or calcitriol]
19 and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin D or
20 hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or
21 controlled trial]. Inclusion criteria will be the ≤ 18 years (children and adolescents) age group. The
22 first search will be done without language restrictions using various combinations of relevant
23 keywords. If any excess relevant keywords are identified during any of the electronic or other
24 searches, search strategies will be modified to incorporate these terms and document the
25 changes; we will also perform a complete updated search on all databases available and identify
26 new studies (if any exist) for inclusion, assess them and incorporate the findings in our review.
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45 **Searching other resources**

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48 To complete the data bank, we will try to detect other potentially relevant studies with a clinical
49 trial design by examining the reference list of the extracted articles in review articles.
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53 **Data collection and analysis**

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Selection of studies

Two review authors (G.A., H.F.) will independently determine studies that should be evaluated further by scanning the abstract, title, or both, of every study retrieved based on inclusion/exclusion criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement through consensus or consultation with a third review author for resolving differences and reaching consensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study selection [25].

Data extraction and management

Two review authors (G.A., H.F.) will independently extract data based on inclusion and exclusion criteria including the method used (randomized clinical trial vs. other studies), and participant and intervention characteristics as described above. In first step the review authors will select articles via keywords or search reference lists of relevant studies, and in the second, full texts of selected articles will be retrieved and screened using inclusion and exclusion criteria. Finally, in third step, we will extract the relevant data from the articles selected in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or consultation with a third review author for resolving differences (F.H.).

Dealing with duplicate and companion publications

In case of duplicate papers or multiple publications of a primary study, we will enhance yield of information by collating all available data and use the most complete dataset aggregated across all known publications.

Quality of assessment

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3 The quality of each included study will be assessed independently by two review authors (G.A.,
4 H.F.). We will assess the quality assessment, focusing on the following criteria: Randomization,
5 allocation concealment, blinding of personnel and of participants, incomplete outcome data,
6 selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve
7 disagreements in quality assessments by consensus, or by consultation with a third review author
8 (F.H.).
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17 **Data synthesis**

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19 We will present data of all included studies and provide a description of results, including
20 population studies, interventions, and outcome in details in both summary tables and the text.
21 Also, a meta-analysis using fixed- or random-effects modeling will be conducted to summarize
22 weighed mean differences and 95% CI in 25-OH-D from baseline to follow-up during the
23 supplementation [27, 28]. We first perform graphical exploration of variability of changes in 25-
24 hydroxyvitamin D levels due to vitamin D doses. A potential nonlinear or linear dose-response
25 relationship between vitamin D supplementation and serum 25-hydroxyvitamin D concentration
26 will be modelled by using restricted cubic splines. We will fit meta-regression models for
27 prediction of linear change in 25-hydroxyvitamin D concentration. We will complete statistical
28 analyses based on the statistical guidelines contained in the latest version of the Cochrane
29 Handbook for Systematic Reviews of Interventions [29].
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46 If we are faced with any missing data in some studies in the process of analysis and data
47 extraction and if we have proper evidence that indicate the randomness of these missing data, we
48 will use data from existence data analysis, otherwise we will obtain the missing data from the
49 study authors if possible; an alternate method where the value of some indices, including mean
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3 or standard deviation are not reported for outcomes is to impute these values by assuming the
4 mean, standard deviation of the missing data to be the average of the mean or standard deviation
5 of data from those studies where this information was given. To investigate the impact of
6 imputation on meta-analyses, we will use sensitivity analysis.
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12 **Assessment of heterogeneity**

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15 Any clinical, methodological or statistical heterogeneity of the data will be investigated via
16 visual inspection of the forest plots and using Chi² test on N-1 degrees of freedom (df), with
17 significance level of $\alpha = 0.1$. If the power of this test is low, we will also calculate heterogeneity
18 by I^2 , a transformation of the square root of the Chi² test divided by its df [30]. If the values of I^2
19 is high we will have greater heterogeneity [31]; should there be heterogeneity in our
20 investigation, we will assess the individual study and subgroup characteristics and perform a
21 sensitivity analyses to clarify the reasons of this heterogeneity [32].
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33 **Assessment of publication biases**

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35 Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33,
36 34]. We will only test for funnel plot asymmetry if the review has included over 10 studies that
37 assess a specific outcome.
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43 **Subgroup analysis**

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45 After the final search and screening, if a sufficient number of studies are available, we will
46 perform subgroup analyses and investigate interactions based on the following: Characteristics of
47 participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level,
48 puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length
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3 of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of
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5 studies.
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7 8 **Sensitivity analysis** 9

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11 We will carry out sensitivity analyses because of the exploring the influence of following factors
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13 on effect sizes and validity of the estimations:
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16 1. Investigation of the impact of quality assessment on the results
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18 2. An analysis of the influence of various characteristics of studies using the following
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20 filters, including duration of intervention, sex, language of publication, country, and dose
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22 of administration
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26 3. An assessment of the effect of different variance imputations.
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28 29 **Discussion** 30

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32 The importance of vitamin D for bone health as well as its role as a hormone in non-skeletal
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34 functions has long been understood. However, to date, no systematic review has been conducted
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36 on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D levels in children and
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38 adolescents worldwide. The findings of this review will provide the existing evidence regarding
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40 the effectiveness of variable doses of vitamin D supplementation in children and adolescents for
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42 improving serum 25-hydroxyvitamin D concentrations. Our research will also provide guidance
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44 to general practitioners, nutritionist, and researchers on the skeletal and extra-skeletal outcomes
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46 and the long term safety of supplementation of various doses of vitamin D in this age group.
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3 **Ethics and dissemination:** Ethics approval is not required because the work is carried out on
4 published documents. The authors will publish findings from this review through peer-reviewed
5 publication or conference presentations.
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17 N M contributed to drafting manuscript and critical revision of manuscript. P M, F H, and F A
18 supervised the study. All authors approved the final version of the manuscript.
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Last Updated September 27, 2017 (n=4019)

PubMed (n=549)

(vitamin D[tiab] OR ergocalciferol[tiab] OR vitamin D2[tiab] OR cholecalciferol[tiab] OR vitamin D3[tiab] OR "ergocalciferols"[MeSH Terms] OR "cholecalciferol"[MeSH Terms]) AND (("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR controlled trial[all fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "intervention study"[All Fields])) AND ("25-hydroxyvitamin D"[tiab] OR "25-hydroxy vitamin D"[tiab] OR hydroxyvitamin D[tiab] OR "25-hydroxyvitamin D2"[tiab] OR "25-hydroxy vitamin D2"[tiab] OR "hydroxyvitamin D2"[tiab] OR "25-hydroxyvitamin D3"[tiab] OR "25-hydroxy vitamin D3"[tiab] OR "hydroxyvitamin D3"[tiab] OR "25OHD"[tiab] OR "25OHD2"[tiab] OR "25OHD3"[tiab] OR "25OH D"[tiab] OR "25OH D3"[tiab] OR "25(OH)D"[tiab] OR "25(OH)D2"[tiab] OR "25(OH)D3"[tiab] OR "25(OH) vitamin D"[tiab] OR "25(OH) vitamin D2"[tiab] OR "25(OH) vitamin D3"[tiab] OR "25OH vitamin D"[tiab] OR "25OH vitamin D3"[tiab] OR 25-hydroxycalciferol[tiab] OR hydroxycholecalciferol[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "25-OH cholecalciferol"[tiab] OR "25OH cholecalciferol"[tiab] OR "25-hydroxy cholecalciferol"[tiab] OR hydroxyergocalciferol[tiab] OR "25- hydroxyergocalciferol"[tiab] OR "25-hydroxy ergocalciferol"[tiab] OR calcitriol[tiab] OR calcidiol[tiab])

Limited by filter in the site to: Age birth to 18 years

Scopus (n=3303)

(TITLE-ABS ("vitamin D") OR TITLE-ABS (ergocalciferol) OR TITLE-ABS (cholecalciferol) OR TITLE-ABS ("vitamin D2") OR TITLE-ABS ("vitamin D3")) AND (TITLE-ABS ("25-hydroxyvitamin D") OR TITLE-ABS ("25-hydroxy vitamin D") OR TITLE-ABS ("hydroxyvitamin D") OR TITLE-ABS ("25-hydroxyvitamin D2") OR TITLE-ABS ("25-hydroxy vitamin D2") OR TITLE-ABS ("hydroxyvitamin D2") OR TITLE-ABS ("25-hydroxyvitamin D3") OR TITLE-ABS ("25-hydroxy vitamin D3") OR TITLE-ABS ("hydroxyvitamin D3") OR TITLE-ABS(25OHD) OR TITLE-ABS(25OHD2) OR TITLE-ABS(25OHD3) OR TITLE-ABS("25-OH-D") OR TITLE-ABS("25-OH-D2") OR TITLE-ABS("25-OH-D3") OR TITLE-ABS ("25(OH)D") OR TITLE-ABS ("25(OH)D2") OR TITLE-ABS ("25(OH)D3") OR TITLE-ABS ("25-OH-vitamin D") OR TITLE-ABS ("25-OH-vitamin D2") OR TITLE-ABS ("25-OH-vitamin D3") OR TITLE-ABS (hydroxycholecalciferol) OR TITLE-ABS (hydroxyergocalciferol) OR TITLE-ABS (calcitriol) OR TITLE-ABS (calcidiol)) AND (ALL ("clinical trial") OR ALL ("controlled trial"))

Limited by the filter in the site: exclusion Adults

ISI Web of Science (n=320)

(TS="vitamin D" OR TS=ergocalciferol OR TS="vitamin D2" OR TS=cholecalciferol OR TS="vitamin D3") AND (TS="25-hydroxyvitamin D" OR TS="25-hydroxy vitamin D" OR TS="hydroxyvitamin D" OR TS="25-hydroxyvitamin D2" OR TS="25-hydroxy vitamin D2" OR TS="hydroxyvitamin D2" OR TS="25-hydroxyvitamin D3" OR TS="25-hydroxy vitamin D3" OR TS="hydroxyvitamin D3" OR TS=25OHD OR TS= 25OHD2 OR TS= 25OHD3 OR TS="25(OH)D" OR TS="25(OH)D2" OR TS="25(OH)D3" OR TS="25OH D" OR TS="25OH D2" OR TS="25OH D3" OR TS="25-OH-vitamin D" OR TS="25-OH-vitamin D2" OR TS="25-OH-vitamin D3" OR TS=hydroxycholecalciferol OR TS=hydroxyergocalciferol OR TS=calcitriol OR TS= calcidiol) AND (TS="clinical trial" OR TS="controlled trial") AND (TS=child* OR TS=adolesc*)

Cochrane Central Register of Controlled Trials (CENTRAL) (n=552)

("vitamin D":ti,ab,kw OR "ergocalciferol":ti,ab,kw OR "vitamin D-2":ti,ab,kw OR "vitamin D2":ti,ab,kw OR "cholecalciferol":ti,ab,kw OR "vitamin D-3":ti,ab,kw OR "vitamin D3":ti,ab,kw) AND

("25-hydroxyvitamin D":ti,ab,kw OR "25-hydroxy vitamin D":ti,ab,kw OR "hydroxyvitamin D":ti,ab,kw OR "25-hydroxyvitamin D2":ti,ab,kw OR "25-hydroxy vitamin D2":ti,ab,kw OR "25-hydroxyvitamin D3":ti,ab,kw OR "25-hydroxyvitamin D-3":ti,ab,kw OR "25-hydroxy vitamin D3":ti,ab,kw OR "hydroxyvitamin D3":ti,ab,kw OR "25OHD":ti,ab,kw OR "25OHD2":ti,ab,kw OR "25OHD3":ti,ab,kw OR "25OH D":ti,ab,kw OR "25OH D3":ti,ab,kw OR "25(OH)D":ti,ab,kw OR "25(OH)D2":ti,ab,kw OR "25(OH)D3":ti,ab,kw OR "25(OH) vitamin D":ti,ab,kw OR "25(OH) vitamin D2":ti,ab,kw OR "25(OH) vitamin D3":ti,ab,kw OR "25OH vitamin D":ti,ab,kw OR "25OH vitamin D3":ti,ab,kw OR "25-hydroxycalciferol":ti,ab,kw OR "hydroxycalciferol":ti,ab,kw OR "25-hydroxycholecalciferol":ti,ab,kw OR "hydroxycholecalciferol":ti,ab,kw OR "25-OH cholecalciferol":ti,ab,kw OR "25-hydroxy cholecalciferol":ti,ab,kw OR "hydroxyergocalciferol":ti,ab,kw OR "25- hydroxyergocalciferol":ti,ab,kw OR "calcitriol":ti,ab,kw OR "calcidiol":ti,ab,kw) AND

("Child":ti,ab,kw OR "adolescence":ti,ab,kw OR "adolescent":ti,ab,kw)

BMJ Open

Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021636.R1
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Nutrition and metabolism, Public health
Keywords:	Vitamin D, 25-hydroxyvitamin D, children, adolescents, meta-analysis

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Manuscripts

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3 **Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in**
4 **children and adolescents: A systematic review and meta-analysis protocol**
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11 Golaleh Asghari¹, Hossein Farhadnejad¹, Farhad Hosseinpanah³, Nazanin Moslehi¹, Parvin

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13 Mirmiran², Fereidoun Azizi⁴
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1 **Abstract**

2 **Introduction:** The importance of vitamin D for bone health as well as its role in non-skeletal
3 functions has long been documented. However, review investigations on the effect of vitamin D
4 supplementation on serum 25-hydroxyvitamin D levels in children and adolescents are scarce.
5 The aim of current study was to assess the impact of various doses of vitamin D supplementation
6 on serum 25(OH)D concentrations in children and adolescents, and to identify relevant
7 determinants of variations in the effect of vitamin D supplementation.

8 **Methods:** PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled
9 Trials (CENTRAL) databases up to the 27-Sep-2017 will systematically be searched for
10 randomized controlled trials of vitamin D supplementation. We considered articles with the
11 following control groups as eligible: placebo control, control group without any
12 supplementation, or a comparative arm investigation. Two reviewers will assess articles for
13 eligibility according to pre-specified selection criteria, after which data extraction and quality
14 appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed
15 using Jadad scales. Meta-analyses will be conducted where appropriate. We will express
16 continuous measures (i.e serum 25(OH)D concentration) as mean differences (MDs) with 95%
17 CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and
18 using Chi² test on N-1 degrees of freedom, with a significance level of $\alpha=0.1$. We will also
19 assess the individual study and subgroup characteristics and perform a sensitivity analysis.
20 Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

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3 21 **Ethics and dissemination:** Ethics approval is not required because the work is carried out on
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5 22 published documents. The authors will publish findings from this review through peer-reviewed
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7 23 publication or conference presentations.
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11 24 **Prospero registration number:** PROSPERO CRD42017067179.
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14 25 **Keywords:** Vitamin D; 25-hydroxyvitamin D; Children; Adolescents; Supplementation;
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16 26 Systematic review
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3 **27 Strengths and limitations of this study**
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- 6 28 • This systematic review will comprehensively assess the effectiveness and safety of
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8 29 various doses of vitamin D supplementation in children and adolescents for improving
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10 30 serum 25(OH)D concentrations.
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14 31 • The study screening, data extraction and quality assessment will be fulfilled by two
15
16 32 independent reviewers.
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19 33 • Based on previous reviews dealing with vitamin D we expect considerable heterogeneity
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21 34 of our data that might be due to variables, including sex, 25(OH)D baseline level, length
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23 35 of intervention, frequency of intervention, doses of vitamin D supplementation.
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27 36 • The systematic review will include only published data.
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37 **Introduction**

38 The importance of vitamin D for bone health as well as its role in non-skeletal functions has long
39 been clarified [1]. Currently, vitamin D deficiency is a global problem, and a recent systematic
40 review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-
41 hydroxyvitamin D [2]. Since childhood and adolescence life cycles increase vitamin
42 requirements for the growth of muscle and bone, vitamin D deficiency is also significantly
43 observed during this period [3]. Low vitamin D status has recently been reported in children and
44 adolescents across countries of the Middle East such as Iran [4, 5], Saudi Arabia [6], Jordan [7],
45 and United Arab Emirates [8], as well as in South East Asia [9, 10], Europe [11], and the United
46 States [12].

47 Serum level of 25(OH)D is a commonly used marker of the long-term vitamin D nutritional
48 status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin
49 D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the
50 cultural beliefs of individuals [3]. Dietary intake of limited foods such as fatty fish, egg yolk,
51 cheese, and fortified foods with vitamin D and also supplementation of vitamin D may increase
52 25(OH)D concentrations [13, 14]. Previous studies in adults showed that baseline 25-
53 hydroxyvitamin D, concurrent calcium intakes, and the level of overweight and obesity are
54 among other factors which may affect 25(OH)D in response to vitamin D supplementation [15].

55 Although many trials have evaluated the effects of vitamin D supplementation on clinical
56 outcomes, few attempts have been made for evaluating the influence of various doses of vitamin
57 D supplementation on serum 25(OH)D levels in children and adolescents [16], a factor crucial
58 for stipulating dietary recommendations. Based on recommendations of the Institute of Medicine
59 (IOM) in 2011, the recommended dietary allowance (RDA) is 600 IU for 9-18-year old children

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3 60 and adolescents [17], whereas based on recommendations of the Endocrine Society, 9-18-year
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5 61 old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000 IU of
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7 62 vitamin D is essential to maintain levels of 25(OH)D > 30 ng/ml [3]; this controversy may be
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10 63 explained by the fact that IOM recommendations are based on achieving the target level of ≥ 20
11
12 64 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on
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14 65 achieving ≥ 30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin
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16 66 D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as
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19 67 obese ones [18], emphasizing the differences in recommendations of these two scientific
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21 68 societies.

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24 69 Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin
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26 70 D, and parathyroid hormone levels [19-21]. A systematic review in adults found that the average
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28 71 increase in serum 25(OH)D concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [22].
29
30 72 Recently a review study from the Middle East and North Africa (MENA) region showed that
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32 73 intakes of intermediate vitamin D dose of 1000–2000 IU daily may be necessary to facilitate for
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34 74 achievement of 25(OH)D level of 20 ng/ml in children and adolescents [16].

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39 75 To the best of our knowledge, to date, no systematic review has been conducted on the effect of
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41 76 vitamin D supplementation on serum 25(OH)D levels in children and adolescents worldwide. In
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43 77 previous original studies also the optimum level of 25(OH)D had not been determined [13, 23,
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45 78 24], and because of lower power, the graded response to vitamin D supplementation could not be
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47 79 explored. This review will therefore aim at determining the effectiveness of various doses of
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49 80 vitamin D supplementation in children and adolescents for improving serum 25(OH)D
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51 81 concentrations and assessing the graded response to vitamin D supplementation. Secondly, we
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3 82 aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by
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5 83 baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.
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8 84 **Methods**

9 85 *Types of studies*

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14 86 We will include randomized controlled trials of vitamin D supplementation with placebo, no
15
16 87 intervention control, or comparative arm studies. Comparative arm is an arm type in which a
17
18 88 group of participants receives another dose of vitamin D, or fortified foods with vitamin D, or
19
20 89 other micronutrients such as vitamin E during the clinical trial. Also, all of included studies must
21
22 90 have reported 25(OH)D level at baseline and at the end of the study.
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26 91 *Types of participants*

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29 92 Healthy children and adolescents (aged ≤ 18 years old) given vitamin D as a preventive measure
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31 93 of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension,
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33 94 and etc.) that have no reason to have altered vitamin D metabolism.
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37 95 Exclusion criteria:

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40 96 a) Rickets in children characterized by low 25(OH)D , below 15 ng/ml with radiologic or
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42 97 laboratory evidence requires higher doses of vitamin D supplementation (higher than those
43
44 98 recommended for the general population).
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47 99 b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or
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49 100 below 30 ml/min), liver disease, heart failure (New York Heart Association class 3 or more)
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3 101 c) Individuals with conditions or on drug therapy that might affect vitamin D metabolism and
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5 102 vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal, malabsorption,
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7 103 bypass surgery)
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11 104 *Types of intervention*
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14 105 Inclusion criteria:
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17 106 Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with
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19 107 or without calcium supplementation
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22 108 Exclusion criteria:
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25 109 a) Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of
26
27 110 supplementation is not recommended for the general population.
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30 111 b) Studies that used vitamin D supplementation given intra muscularly
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33 112 c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin
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35 113 cannot be defined accurately
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38 114 **Search methods for identification of studies**
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41 115 **Electronic searches**
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44 116 We will perform a systematic search of published randomized trials on vitamin D
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46 117 supplementation in subjects aged ≤ 18 years old in PubMed, Scopus, ISI Web of Science, and
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48 118 Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017 using
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50 119 eligible keywords in titles or abstracts (for details on search strategies see Supplementary File 1),
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52 120 using the following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or
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3 121 calcitriol] and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin
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5 122 D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or
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7
8 123 controlled trial]. Inclusion criteria will be the ≤ 18 years (children and adolescents) age group. The
9
10 124 first search will be done without language restrictions using various combinations of relevant
11
12 125 keywords. We will also perform a complete updated search on all databases available and
13
14 126 identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our
15
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17 127 review.

128 **Searching other resources**

129 To complete the data bank, we will use snowballing techniques to complement the database
130 searches by screening the reference lists of included articles for relevant studies.

131 **Data collection and analysis**

132 **Selection of studies**

133 Two authors (G.A., H.F.) will independently determine studies that should be evaluated further
134 by scanning the title, abstract, or both, of every study retrieved based on inclusion/exclusion
135 criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement
136 through consensus or consultation with a third review author for resolving differences and
137 reaching consensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic
138 Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study
139 selection [25].

140 **Data extraction and management**

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3 141 In the first step, two authors (G.A., H.F.) will independently select articles by title and abstract or
4
5 142 search reference lists of relevant studies, and in the second, full texts of selected articles will be
6
7 143 retrieved and screened using inclusion and exclusion criteria (study design, participants, and
8
9 144 intervention). Finally, in the third step, we will extract the relevant data from the selected articles
10
11 145 in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or
12
13 146 consultation with a third author for resolving differences (F.H.).
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17 147 **Dealing with duplicate and companion publications**

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20 148 In case of duplicate papers or multiple publications of a primary study, we will enhance yield of
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22 149 information by collating all available data and use the most complete dataset aggregated across
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24 150 all known publications.
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28 151 **Quality of assessment**

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31 152 The quality of each included study will be assessed independently by two authors (G.A., H.F.).
32
33 153 We will assess the quality assessment, focusing on the following criteria: Randomization,
34
35 154 allocation concealment, blinding of personnel and of participants, incomplete outcome data,
36
37 155 selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve
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39 156 disagreements in quality assessments by consensus, or by consultation with a third author (F.H.).
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43 157 **Data synthesis**

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46 158 We will present data of all included studies and provide a description of results, including study
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48 159 population, interventions, and outcome in details in both summary tables and the text. Also, a
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50 160 meta-analysis using fixed- or random-effects modeling will be conducted to summarize weighed
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52 161 mean differences and 95% CI in 25(OH)D from baseline to follow-up during the
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3 162 supplementation [27, 28]. We first perform graphical exploration of variability of changes in
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5 163 25(OH)D levels due to vitamin D doses. A potential nonlinear or linear dose-response
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7 164 relationship between vitamin D supplementation and serum 25(OH)D concentration will be
8
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10 165 modelled by using restricted cubic splines. We will fit meta-regression models for prediction of
11
12 166 linear change in 25(OH)D concentration. We will complete statistical analyses based on the
13
14 167 statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic
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16 168 Reviews of Interventions [29].

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20 169 If we are faced with any missing data in some studies in the process of analysis and data
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22 170 extraction and if we have proper evidence that indicate the randomness of these missing data, we
23
24 171 will use data from existence data analysis, otherwise we will obtain the missing data from the
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26 172 study authors if possible; an alternate method where the value of some indices, including mean
27
28 173 or standard deviation are not reported for outcomes is to impute these values by assuming the
29
30 174 mean, standard deviation of the missing data to be the average of the mean or standard deviation
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32 175 of data from those studies where this information was given. To investigate the impact of
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34 176 imputation on meta-analyses, we will use sensitivity analysis.

35 36 37 38 39 177 **Assessment of heterogeneity**

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42 178 Any clinical, methodological or statistical heterogeneity of the data will be investigated via
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44 179 visual inspection of the forest plots and using Chi^2 test on $N-1$ degrees of freedom (df), with
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46 180 significance level of $\alpha = 0.1$. If the power of this test is low, we will also calculate heterogeneity
47
48 181 by I^2 , a transformation of the square root of the Chi^2 test divided by its df [30]. If the values of I^2
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50 182 is high we will have greater heterogeneity [31]; should there be heterogeneity in our
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3 183 investigation, we will assess the individual study and subgroup characteristics and perform a
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5 184 sensitivity analyses to clarify the reasons of this heterogeneity [32].
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8 185 **Assessment of publication biases**

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11 186 Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33,
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13 187 34]. We will only test for funnel plot asymmetry if the review has included over 10 studies that
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16 188 assess a specific outcome.
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18 189 **Subgroup analysis**

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22 190 After the final search and screening, if a sufficient number of studies are available, we will
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24 191 perform subgroup analyses and investigate interactions based on the following: Characteristics of
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26 192 participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level,
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28 193 puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length
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30 194 of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of
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33 195 studies.
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35 196 **Sensitivity analysis**

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39 197 We will carry out sensitivity analyses because of the exploring the influence of following factors
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41 198 on effect sizes and validity of the estimations:
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- 44 199 1. Investigation of the impact of quality assessment on the results
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46 200 2. An analysis of the influence of various characteristics of studies using the following
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48 201 filters, including duration of intervention, sex, language of publication, country, and dose
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50 202 of administration
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52 203 3. An assessment of the effect of different variance imputations.
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3 204 **Patient and public involvement**
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6 205 Patients and/or public are not involved in this study.
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9 206 **Summary statement**
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12 207 The findings of this review will provide the existing evidence regarding the effectiveness of
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14 208 various doses of vitamin D supplementation in children and adolescents for improving serum
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16 209 25(OH)D concentrations. Our research will also provide guidance to general practitioners,
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18 210 nutritionist, and researchers on the skeletal and extra-skeletal outcomes and the long term safety
19
20 211 of supplementation of various doses of vitamin D in this age group.
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24 212 **Ethics and dissemination:** Ethics approval is not required because the work is carried out on
25
26 213 published documents. The authors will publish findings from this review through peer-reviewed
27
28 214 publication or conference presentations.
29
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31
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39 218 the protocol. NM designed the search strategies. PM proposed some important advice for the
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41 219 study design and revision PM and FA aided in developing the research questions. All authors
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43 220 critically revised the draft of the manuscript and approved its final version. GA and HF are the
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3 225 **Provenance and peer review:** Not commissioned; externally peer reviewed.
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For peer review only

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Last Updated September 27, 2017 (n=4019)

PubMed (n=549)

(vitamin D[tiab] OR ergocalciferol[tiab] OR vitamin D2[tiab] OR cholecalciferol[tiab] OR vitamin D3[tiab] OR "ergocalciferols"[MeSH Terms] OR "cholecalciferol"[MeSH Terms]) AND (("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]) OR controlled trial[all fields] OR ("clinical trial"[Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "intervention study"[All Fields])) AND ("25-hydroxyvitamin D"[tiab] OR "25-hydroxy vitamin D"[tiab] OR hydroxyvitamin D[tiab] OR "25-hydroxyvitamin D2"[tiab] OR "25-hydroxy vitamin D2"[tiab] OR "hydroxyvitamin D2"[tiab] OR "25-hydroxyvitamin D3"[tiab] OR "25-hydroxy vitamin D3"[tiab] OR "hydroxyvitamin D3"[tiab] OR "25OHD"[tiab] OR "25OHD2"[tiab] OR "25OHD3"[tiab] OR "25OH D"[tiab] OR "25OH D3"[tiab] OR "25(OH)D"[tiab] OR "25(OH)D2"[tiab] OR "25(OH)D3"[tiab] OR "25(OH) vitamin D"[tiab] OR "25(OH) vitamin D2"[tiab] OR "25(OH) vitamin D3"[tiab] OR "25OH vitamin D"[tiab] OR "25OH vitamin D3"[tiab] OR 25-hydroxycalciferol[tiab] OR hydroxycholecalciferol[tiab] OR "25-hydroxycholecalciferol"[tiab] OR "25-OH cholecalciferol"[tiab] OR "25OH cholecalciferol"[tiab] OR "25-hydroxy cholecalciferol"[tiab] OR hydroxyergocalciferol[tiab] OR "25- hydroxyergocalciferol"[tiab] OR "25-hydroxy ergocalciferol"[tiab] OR calcitriol[tiab] OR calcidiol[tiab])

Limited by filter in the site to: Age birth to 18 years

Scopus (n=3303)

(TITLE-ABS ("vitamin D") OR TITLE-ABS (ergocalciferol) OR TITLE-ABS (cholecalciferol) OR TITLE-ABS ("vitamin D2") OR TITLE-ABS ("vitamin D3")) AND (TITLE-ABS ("25-hydroxyvitamin D") OR TITLE-ABS ("25-hydroxy vitamin D") OR TITLE-ABS ("hydroxyvitamin D") OR TITLE-ABS ("25-hydroxyvitamin D2") OR TITLE-ABS ("25-hydroxy vitamin D2") OR TITLE-ABS ("hydroxyvitamin D2") OR TITLE-ABS ("25-hydroxyvitamin D3") OR TITLE-ABS ("25-hydroxy vitamin D3") OR TITLE-ABS ("hydroxyvitamin D3") OR TITLE-ABS(25OHD) OR TITLE-ABS(25OHD2) OR TITLE-ABS(25OHD3) OR TITLE-ABS("25-OH-D") OR TITLE-ABS("25-OH-D2") OR TITLE-ABS("25-OH-D3") OR TITLE-ABS ("25(OH)D") OR TITLE-ABS ("25(OH)D2") OR TITLE-ABS ("25(OH)D3") OR TITLE-ABS ("25-OH-vitamin D") OR TITLE-ABS ("25-OH-vitamin D2") OR TITLE-ABS ("25-OH-vitamin D3") OR TITLE-ABS (hydroxycholecalciferol) OR TITLE-ABS (hydroxyergocalciferol) OR TITLE-ABS (calcitriol) OR TITLE-ABS (calcidiol)) AND (ALL ("clinical trial") OR ALL ("controlled trial"))

Limited by the filter in the site: exclusion Adults

ISI Web of Science (n=320)

(TS="vitamin D" OR TS=ergocalciferol OR TS="vitamin D2" OR TS=cholecalciferol OR TS="vitamin D3") AND (TS="25-hydroxyvitamin D" OR TS="25-hydroxy vitamin D" OR TS="hydroxyvitamin D" OR TS="25-hydroxyvitamin D2" OR TS="25-hydroxy vitamin D2" OR TS="hydroxyvitamin D2" OR TS="25-hydroxyvitamin D3" OR TS="25-hydroxy vitamin D3" OR TS="hydroxyvitamin D3" OR TS=25OHD OR TS= 25OHD2 OR TS= 25OHD3 OR TS="25(OH)D" OR TS="25(OH)D2" OR TS="25(OH)D3" OR TS="25OH D" OR TS="25OH D2" OR TS="25OH D3" OR TS="25-OH-vitamin D" OR TS="25-OH-vitamin D2" OR TS="25-OH-vitamin D3" OR TS=hydroxycholecalciferol OR TS=hydroxyergocalciferol OR TS= calcitriol OR TS= calcidiol) AND (TS="clinical trial" OR TS="controlled trial") AND (TS=child* OR TS=adolesc*)

Cochrane Central Register of Controlled Trials (CENTRAL) (n=552)

("vitamin D":ti,ab,kw OR "ergocalciferol":ti,ab,kw OR "vitamin D-2":ti,ab,kw OR "vitamin D2":ti,ab,kw OR "cholecalciferol":ti,ab,kw OR "vitamin D-3":ti,ab,kw OR "vitamin D3":ti,ab,kw) AND

("25-hydroxyvitamin D":ti,ab,kw OR "25-hydroxy vitamin D":ti,ab,kw OR "hydroxyvitamin D":ti,ab,kw OR "25-hydroxyvitamin D2":ti,ab,kw OR "25-hydroxy vitamin D2":ti,ab,kw OR "25-hydroxyvitamin D3":ti,ab,kw OR "25-hydroxyvitamin D-3":ti,ab,kw OR "25-hydroxy vitamin D3":ti,ab,kw OR "hydroxyvitamin D3":ti,ab,kw OR "25OHD":ti,ab,kw OR "25OHD2":ti,ab,kw OR "25OHD3":ti,ab,kw OR "25OH D":ti,ab,kw OR "25OH D3":ti,ab,kw OR "25(OH)D":ti,ab,kw OR "25(OH)D2":ti,ab,kw OR "25(OH)D3":ti,ab,kw OR "25(OH) vitamin D":ti,ab,kw OR "25(OH) vitamin D2":ti,ab,kw OR "25(OH) vitamin D3":ti,ab,kw OR "25OH vitamin D":ti,ab,kw OR "25OH vitamin D3":ti,ab,kw OR "25-hydroxycalciferol":ti,ab,kw OR "hydroxycalciferol":ti,ab,kw OR "25-hydroxycholecalciferol":ti,ab,kw OR "hydroxycholecalciferol":ti,ab,kw OR "25-OH cholecalciferol":ti,ab,kw OR "25-hydroxy cholecalciferol":ti,ab,kw OR "hydroxyergocalciferol":ti,ab,kw OR "25- hydroxyergocalciferol":ti,ab,kw OR "calcitriol":ti,ab,kw OR "calcidiol":ti,ab,kw) AND

("Child":ti,ab,kw OR "adolescence":ti,ab,kw OR "adolescent":ti,ab,kw)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line/page numbers
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3, line 24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 13, lines 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 13, lines 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 6, lines 52-74
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pages 6-7, lines 79-83
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 7-8, lines 85-113
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 8, lines 116-119
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pages 8-9, lines 116-130
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 10, lines 141-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 10, lines 141-146
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 10, lines 141-146
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 10-11, lines 158-162
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7, lines 89-90
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 10, lines 152-156
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pages 10-11, lines 158-176
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	Pages 11-12, lines 178-184
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 12, lines 189-203
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12, lines 186-188
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10, lines 152-156

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in children and adolescents: A systematic review and meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021636.R2
Article Type:	Protocol
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Nutrition and metabolism, Public health
Keywords:	Vitamin D, 25-hydroxyvitamin D, children, adolescents, meta-analysis

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Manuscripts

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3 **Effect of vitamin D supplementation on serum 25-hydroxyvitamin D concentration in**
4 **children and adolescents: A systematic review and meta-analysis protocol**
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11 Golaleh Asghari¹, Hossein Farhadnejad¹, Farhad Hosseinpanah³, Nazanin Moslehi¹, Parvin

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13 Mirmiran², Fereidoun Azizi⁴
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1 **Abstract**

2 **Introduction:** The importance of vitamin D for bone health as well as its role in non-skeletal
3 functions has long been documented. However, review investigations on the effect of vitamin D
4 supplementation on serum 25-hydroxyvitamin D (25(OH)D) levels in children and adolescents
5 are scarce. The aim of current study was to assess the impact of various doses of vitamin D
6 supplementation on serum 25(OH)D concentrations in children and adolescents, and to identify
7 relevant determinants of variations in the effect of vitamin D supplementation.

8 **Methods:** PubMed, Scopus, ISI Web of Science, and Cochrane Central Register of Controlled
9 Trials (CENTRAL) databases up to the 27-Sep-2017 will systematically be searched for
10 randomized controlled trials of vitamin D supplementation. We considered articles with the
11 following control groups as eligible: Placebo control, control group without any
12 supplementation, or a comparative arm investigation. Two reviewers will assess articles for
13 eligibility according to pre-specified selection criteria, after which data extraction and quality
14 appraisal will be conducted by 2 independent reviewers. The quality assessment will be assessed
15 using Jadad scales. Meta-analyses will be conducted where appropriate. We will express
16 continuous measures (i.e serum 25(OH)D concentration) as mean differences (MDs) with 95%
17 CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and
18 using Chi² test on N-1 degrees of freedom, with a significance level of $\alpha=0.1$. We will also
19 assess the individual study and subgroup characteristics and perform a sensitivity analysis.
20 Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test.

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3 21 **Ethics and dissemination:** Ethics approval is not required because the work will be carried out
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5 22 on published documents. The authors will publish findings from this review through peer-
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7 23 reviewed publication or conference presentations.
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11 24 **Prospero registration number:** PROSPERO CRD42017067179.
12

13
14 25 **Keywords:** Vitamin D; 25-hydroxyvitamin D; Children; Adolescents; Supplementation;
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16 26 Systematic review
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For peer review only

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3 27 **Strengths and limitations of this study**
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- 6 28 • This systematic review will comprehensively assess the effectiveness and safety of
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8 29 various doses of vitamin D supplementation in children and adolescents for improving
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10 30 serum 25(OH)D concentrations.
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14 31 • The study screening, data extraction and quality assessment will be fulfilled by two
15
16 32 independent reviewers.
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19 33 • Based on previous reviews dealing with vitamin D, we expect considerable heterogeneity
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21 34 of our data, which might be due to variables, including sex, 25(OH)D baseline level,
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23 35 length of intervention, frequency of intervention, doses of vitamin D supplementation.
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27 36 • The systematic review will include only published data.
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37 Introduction

38 The importance of vitamin D for bone health as well as its role in non-skeletal functions has long
39 been clarified [1]. Currently, vitamin D deficiency is a global problem, and a recent systematic
40 review found that about 37% of the studies reported an average of less than 20 ng/ml for 25-
41 hydroxyvitamin D (25(OH)D) [2]. Since during childhood and adolescence, vitamin D
42 requirements increase for the growth of muscle and bone, vitamin D deficiency is often observed
43 during this period [3]. Low vitamin D status has recently been reported in children and
44 adolescents across countries of the Middle East such as Iran [4, 5], Saudi Arabia [6], Jordan [7],
45 and United Arab Emirates [8], as well as in South East Asia [9, 10], Europe [11], and the United
46 States [12].

47 Serum level of 25(OH)D is a commonly used marker of the long-term vitamin D nutritional
48 status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin
49 D, which is dependent on skin color, latitude, season, lifestyle, and dress codes based on the
50 cultural beliefs of individuals [3]. Dietary intakes of limited foods such as fatty fish, egg yolk,
51 cheese, and fortified foods with vitamin D and also supplementation of vitamin D may increase
52 25(OH)D concentrations [13, 14]. Previous studies in adults showed that baseline 25-
53 hydroxyvitamin D, concurrent calcium intakes, and levels of overweight and obesity are among
54 other factors which may affect 25(OH)D in response to vitamin D supplementation [15].
55 Although many trials have evaluated the effects of vitamin D supplementation on clinical
56 outcomes, few attempts have been made to evaluate the effects of various doses of vitamin D
57 supplementation on serum 25(OH)D levels in children and adolescents [16], a factor crucial to
58 stipulating dietary recommendations. Based on recommendations of the Institute of Medicine
59 (IOM) in 2011, the recommended daily dietary allowance (RDA) is 600 IU for 9-18-year old

1
2
3 60 children and adolescents [17], whereas based on recommendations of the Endocrine Society, 9-
4
5 61 18-year old children and adolescents need at least 600 IU of vitamin D daily, and at least 1000
6
7 62 IU of vitamin D is essential to maintain levels of 25(OH)D > 30 ng/ml [3]; this controversy may
8
9
10 63 be explained by the fact that IOM recommendations are based on achieving the target level of
11
12 64 ≥ 20 ng/ml for 25-hydroxyvitamin D, while the Endocrine society recommendation is based on
13
14 65 achieving ≥ 30 ng/ml. The Society for Adolescent Health and Medicine suggests 600 IU vitamin
15
16 66 D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as
17
18 67 obese adolescents [18], emphasizing the differences in recommendations of these two scientific
19
20
21 68 societies.

22
23
24 69 Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin
25
26 70 D, and parathyroid hormone levels [19-21]. A systematic review in adults found that the average
27
28 71 increase in serum 25(OH)D concentrations was 0.78 ng/ml per mcg of vitamin D3 per day [22].
29
30
31 72 Recently a review study from the Middle East and North Africa (MENA) region showed that
32
33 73 intakes of an intermediate vitamin D dose of 1000–2000 IU daily may be necessary to
34
35 74 achievement of level in 20 ng/ml 25(OH)D in children and adolescents [16].

36
37
38
39 75 To the best of our knowledge, to date, no systematic review has been conducted on the effect of
40
41 76 vitamin D supplementation on serum 25(OH)D levels in children and adolescents worldwide. In
42
43 77 previous original studies also the optimum level of 25(OH)D had not been determined [13, 23,
44
45 78 24], and because of lower power, the graded response to vitamin D supplementation could not be
46
47 79 explored. This review will therefore aim at determining the effectiveness of various doses of
48
49
50 80 vitamin D supplementation in children and adolescents for improving serum 25(OH)D
51
52 81 concentrations and assessing the graded response to vitamin D supplementation. Secondly, we

1
2
3 82 aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by
4
5 83 baseline vitamin D status, sex, body mass index, puberty status, or the type of vitamin D given.
6
7

8 84 **Methods**

9 85 *Types of studies*

10
11 86 We will include randomized controlled trials of vitamin D supplementation with one of the
12
13
14 87 following: Placebo, no control, or comparative arm studies. Comparative arm is an arm type in
15
16
17 88 which a group of participants receives another dose of vitamin D, or fortified foods with vitamin
18
19 89 D, or other micronutrients such as vitamin E during the clinical trial. Also, all the included
20
21
22 90 studies must have reported 25(OH)D level at baseline and at the end of the study.
23
24
25

26 91 *Types of participants*

27
28
29 92 Healthy children and adolescents (aged ≤ 18 years old) given vitamin D as a preventive measure
30
31
32 93 of certain diseases or individuals with mild diseases (such as flu, obesity, asthma, hypertension,
33
34 94 and etc.) that have no reason to have altered vitamin D metabolism.
35
36

37 95 Exclusion criteria:

- 38
39
40 96 a) Rickets in children characterized by low 25(OH)D, (below 15 ng/ml) with radiologic or
41
42 97 laboratory evidence requiring higher doses of vitamin D supplementation (higher than those
43
44 98 recommended for the general population).
45
46
47 99 b) Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or
48
49
50 100 below 30 ml/min), liver disease, heart failure (New York Heart Association class 3 or more)
51
52
53
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57
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2
3 101 c) Individuals with conditions or on drug therapy both of which may affect vitamin D
4
5 102 metabolism and vitamin D binding protein /metabolism (anticonvulsants, steroids, anti-fungal,
6
7 103 malabsorption, bypass surgery)
8
9

10
11 104 *Types of intervention*
12

13
14 105 Inclusion criteria:
15

16
17 106 Vitamin D (D2 or D3) supplementation of any dose, given orally, daily, weekly or monthly, with
18
19 107 or without calcium supplementation
20

21
22 108 Exclusion criteria:
23

24
25 109 a) Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of
26
27 110 supplementation is not recommended for the general population.
28

29
30 111 b) Studies that used vitamin D supplementation given intra muscularly
31

32
33 112 c) Studies that used vitamin D supplementation as fortified foods as the amount of vitamin
34
35 113 cannot be defined accurately
36
37

38 114 **Patient and public involvement**
39

40
41 115 Patients and/or public are not involved in this study.
42
43

44 116
45
46

47 117 **Search methods for identification of studies**
48

49
50 118 **Electronic searches**
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52
53
54
55

1
2
3 119 We will perform a systematic search of published randomized trials on vitamin D
4
5 120 supplementation in subjects aged ≤ 18 years in PubMed, Scopus, ISI Web of Science, and
6
7
8 121 Cochrane Central Register of Controlled Trials (CENTRAL) databases up to 27-Sep-2017, using
9
10 122 eligible keywords in titles or abstracts (for details on search strategies see Supplementary File 1),
11
12 123 using the following search terms: [Vitamin D or ergocalciferol or cholecalciferol or calcidiol or
13
14 124 calcitriol] and [25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin
15
16 125 D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol] and [clinical trial or
17
18 126 controlled trial]. Inclusion criteria will be the ≤ 18 year (children and adolescents age group). The
19
20 127 first search will be done without language restrictions using various combinations of relevant
21
22 128 keywords. We will also perform a complete updated search on all databases available and
23
24 129 identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our
25
26 130 review.

31 **Searching other resources**

32
33
34 132 To complete the data bank, we will use snowballing techniques to complement the database
35
36 133 searches by screening the reference lists of included articles for relevant studies.

39 **Data collection and analysis**

42 **Selection of studies**

43
44
45 136 Two authors (G.A., H.F.) will independently determine studies that should be evaluated further
46
47 137 by scanning the title, abstract, or both, of every study retrieved based on inclusion/exclusion
48
49 138 criteria. We will assess all potentially relevant articles as full texts and resolve any disagreement
50
51 139 through consensus or consultation with a third review author for resolving differences and
52
53 140 reaching consensus (F.H.). Also, an adapted PRISMA (Preferred Reporting Items for Systematic
54
55

1
2
3 141 Reviews and Meta-Analyses) flow diagram will be presented to indicate the process of study
4
5 142 selection [25].
6
7

8 143 **Data extraction and management**

9
10 144 In the first step, two authors (G.A., H.F.) will independently select articles by title and abstract or
11
12 145 search reference lists of relevant studies, and in the second, full texts of selected articles will be
13
14 146 retrieved and screened using inclusion and exclusion criteria (study design, participants, and
15
16 147 intervention). Finally, in the third step, we will extract the relevant data from the selected articles
17
18 148 in a structured data bank (G.A., H.F.). We will resolve any disagreement through consensus or
19
20 149 consultation with a third author for resolving differences (F.H.).
21
22
23
24

25 150 **Dealing with duplicate and companion publications**

26
27
28 151 In case of duplicate papers or multiple publications of a primary study, we will enhance yield of
29
30 152 information by collating all available data and use the most complete dataset aggregated across
31
32 153 all known publications.
33
34
35

36 154 **Quality assessment**

37
38
39 155 The quality of each included study will be assessed independently by two authors (G.A., H.F.).
40
41 156 We will assess the quality assessment, focusing on the following criteria: Randomization,
42
43 157 allocation concealment, blinding of personnel and of participants, incomplete outcome data,
44
45 158 selective reporting and other potential sources of bias using Jadad scales [26]. We will resolve
46
47 159 disagreements in quality assessments by consensus, or by consultation with a third author (F.H.).
48
49
50

51 160 **Data synthesis**

1
2
3 161 We will present data of all included studies and provide a description of results, including study
4
5 162 population, intervention, and outcome in details in both summary tables and the text. Also, a
6
7 163 meta-analysis using fixed- or random-effects modeling will be conducted to summarize weighed
8
9 164 mean differences and 95% CI in 25(OH)D from baseline to follow-up during the
10
11 165 supplementation [27, 28]. We will first perform graphical exploration of variability of changes in
12
13 166 25(OH)D levels due to vitamin D doses. A potential nonlinear or linear dose-response
14
15 167 relationship between vitamin D supplementation and serum 25(OH)D concentration will be
16
17 168 modelled by using restricted cubic splines. We will fit meta-regression models for prediction of
18
19 169 linear change in 25(OH)D concentration. We will complete statistical analyses based on the
20
21 170 statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic
22
23 171 Reviews of Interventions [29].
24
25
26
27
28

29 172 If faced with any missing data in some studies in the process of analysis and data extraction and
30
31 173 if we have proper evidence that indicates the randomness of these missing data, we will use data
32
33 174 from existing data analyses, otherwise we will obtain the missing data from the study authors if
34
35 175 possible; an alternate method where the value of some indices, including mean or standard
36
37 176 deviation are not reported for outcomes is to impute these values by assuming the mean, standard
38
39 177 deviation of the missing data to be the average of the mean or standard deviation of data from
40
41 178 those studies where this information was given. To investigate the impact of imputation on meta-
42
43 179 analyses, we will use sensitivity analysis.
44
45
46
47

48 180 **Assessment of heterogeneity**

49
50

51 181 Any clinical, methodological or statistical heterogeneity of the data will be investigated via
52
53 182 visual inspection of the forest plots and using Chi^2 test with N-1 degrees of freedom (df), and
54
55

1
2
3 183 significance level of $\alpha = 0.1$. If the power of this test is low, we will also calculate heterogeneity
4
5 184 by I^2 , a transformation of the square root of the Chi^2 test divided by its df [30]. If the values of I^2
6
7
8 185 is high we will have greater heterogeneity [31]; should there be heterogeneity in our
9
10 186 investigation, we will assess the individual study and subgroup characteristics and perform a
11
12 187 sensitivity analysis to clarify the reasons of this heterogeneity [32].
13
14

15 188 **Assessment of publication biases**

16
17
18 189 Publication bias will be assessed using funnel plot and statistical analysis of Eggers' test [33,
19
20 190 34]. We will only test for funnel plot asymmetry if our review includes over 10 studies that
21
22
23 191 assess a specific outcome.
24
25

26 192 **Subgroup analysis**

27
28
29 193 After the final search and screening, if a sufficient number of studies are available, we will
30
31 194 perform subgroup analyses and investigate interactions based on the following: Characteristics of
32
33 195 participants, intervention, and outcomes including sex, 25-hydroxy vitamin D baseline level,
34
35
36 196 puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length
37
38 197 of intervention, frequency of intervention, doses of vitamin D supplementation, and quality of
39
40 198 studies.
41
42

43 199 **Sensitivity analysis**

44
45
46 200 We will carry out sensitivity analyses because of the exploring the influence of following factors
47
48 201 on effect sizes and validity of the estimations:
49
50

- 51 202 1. Investigation of the impact of quality assessment on the results
- 52
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- 1
2
3 203 2. An analysis of the influence of various characteristics of studies using the following
4
5 204 filters: Duration of intervention, sex, language of publication, country, and dose of
6
7 administration
8 205
9
10 206 3. An assessment of the effect of different variance imputations.
11
12

13 207 **Ethics and dissemination:** Ethics approval is not required because the work is carried out on
14
15 208 published documents. The authors will publish findings from this review through peer-reviewed
16
17 209 publication or conference presentations.
18
19

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29
30 214 critically revised the draft of the manuscript and approved its final version. GA and HF are the
31
32 215 guarantors of the review.
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35 216
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39
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41
42

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44
45

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Line/page numbers
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 3, line 24
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 13, lines 217-221
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	No
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 13, lines 222-223
Sponsor	5b	Provide name for the review funder and/or sponsor	No
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	No
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 6, lines 52-74
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Pages 6-7, lines 79-83
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Pages 7-8, lines 85-113
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 8, lines 116-119
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Pages 8-9, lines 116-130
Study records:			

Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 10, lines 141-150
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 10, lines 141-146
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 10, lines 141-146
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Pages 10-11, lines 158-162
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7, lines 89-90
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 10, lines 152-156
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Pages 10-11, lines 158-176
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	Pages 11-12, lines 178-184
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 12, lines 189-203
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	No
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 12, lines 186-188
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 10, lines 152-156

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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