

# BMJ Open 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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## ABSTRACT

**Introduction** The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been documented. However, review investigations on the effect of vitamin D supplementation on serum 25-hydroxyvitamin D (25(OH)D) levels in children and adolescents are scarce. The aims of the current study were to assess the impact of various doses of vitamin D supplementation on serum 25(OH)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 databases up to 27 September 2017 will systematically be searched for randomised controlled trials of vitamin D supplementation. We considered articles with the following control groups as eligible: placebo control, control group without any supplementation or a comparative arm investigation. Two reviewers will assess articles for eligibility according to prespecified selection criteria, after which data extraction and quality appraisal will be conducted by two independent reviewers. The quality assessment will be assessed using the Jadad scale. Meta-analyses will be conducted where appropriate. We will express continuous measures (ie, serum 25(OH)D concentration) as mean differences with 95% CIs. Heterogeneity of the data will be investigated via visual inspection of the forest plots and using  $\chi^2$  test on N-1 df, with a significance level of  $\alpha=0.1$ . We will also assess individual study and subgroup characteristics and perform a sensitivity analysis. Publication bias will be assessed using funnel plot and statistical analysis of Egger's test.

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

**PROSPERO registration number** CRD42017067179.

## INTRODUCTION

The importance of vitamin D for bone health as well as its role in non-skeletal functions has long been clarified.<sup>1</sup> Currently, vitamin D

## Strengths and limitations of this study

- This systematic review will comprehensively assess the effectiveness and safety of various doses of vitamin D supplementation in children and adolescents in improving serum 25-hydroxyvitamin D (25(OH)D) concentrations.
- The study screening, data extraction and quality assessment will be fulfilled by two independent reviewers.
- Based on previous reviews dealing with vitamin D, we expect considerable heterogeneity of our data, which might be due to variables that include sex, 25(OH)D baseline level, length of intervention, frequency of intervention and doses of vitamin D supplementation.
- The systematic review will include only published data.

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 (25(OH)D).<sup>2</sup> Since during childhood and adolescence vitamin D requirements increase for the growth of muscles and bones, vitamin D deficiency is often observed during this period.<sup>3</sup> Low vitamin D status has recently been reported in children and adolescents across countries of the Middle East such as Iran,<sup>4 5</sup> Saudi Arabia,<sup>6</sup> Jordan<sup>7</sup> and the United Arab Emirates,<sup>8</sup> as well as in South-East Asia,<sup>9 10</sup> Europe<sup>11</sup> and the USA.<sup>12</sup>

The serum level of 25(OH)D is a commonly used marker of the long-term vitamin D nutritional status of individuals. Exposure to sunlight is the most important factor in the synthesis of vitamin D, which is dependent on skin colour, latitude, season, lifestyle and dress codes based on the cultural beliefs of

individuals.<sup>3</sup> Dietary intake of limited foods such as fatty fish, egg-yolk, cheese and fortified foods with vitamin D and also supplementation of vitamin D may increase 25(OH)D concentrations.<sup>13 14</sup> Previous studies in adults showed that baseline 25(OH)D, concurrent calcium intake and levels of overweight and obesity are among other factors which may affect 25(OH)D in response to vitamin D supplementation.<sup>15</sup> Although many trials have evaluated the effects of vitamin D supplementation on clinical outcomes, few attempts have been made to evaluate the effects of various doses of vitamin D supplementation on serum 25(OH)D levels in children and adolescents,<sup>16</sup> a factor crucial to stipulating dietary recommendations. Based on the recommendations of the Institute of Medicine (IOM) in 2011, the recommended daily dietary allowance is 600 IU for children and adolescents aged 9–18 years old,<sup>17</sup> whereas based on the recommendations of the Endocrine Society, children and adolescents aged 9–18 years old need at least 600 IU of vitamin D daily, and at least 1000 IU of vitamin D is essential to maintain levels of 25(OH)D >30 ng/mL<sup>3</sup>; this controversy may be explained by the fact that the IOM recommendations are based on achieving the target level of  $\geq 20$  ng/mL for 25(OH)D, while the Endocrine Society recommendations are based on achieving  $\geq 30$  ng/mL. The Society for Adolescent Health and Medicine suggests 600 IU vitamin D for healthy adolescents and at least 1000 IU for those at risk of vitamin D deficiency, such as obese adolescents,<sup>18</sup> emphasising the differences in recommendations of these two scientific societies.

Previous studies have shown that obesity might also influence 25(OH)D, 1,25-hydroxyvitamin D and parathyroid hormone levels.<sup>19–21</sup> A systematic review in adults found that the average increase in serum 25(OH)D concentrations was 0.78 ng/mL per microgram of vitamin D<sub>3</sub> per day.<sup>22</sup> Recently a review study from the Middle East and North Africa regions showed that intake of an intermediate vitamin D dose of 1000–2000 IU daily may be necessary to achieve a 20 ng/mL 25(OH)D level in children and adolescents.<sup>16</sup>

To the best of our knowledge, to date, no systematic review has been conducted on the effect of vitamin D supplementation on serum 25(OH)D levels in children and adolescents worldwide. In previous original studies also the optimum level of 25(OH)D had not been determined,<sup>13 23 24</sup> and because of lower power the graded response to vitamin D supplementation could not be explored. This review will therefore aim at determining the effectiveness of various doses of vitamin D supplementation in children and adolescents in improving serum 25(OH)D concentrations and assessing the graded response to vitamin D supplementation. Second, we aimed to determine if the effect of vitamin D supplementation on serum 25(OH)D varies by baseline vitamin D status, sex, body mass index, puberty status or the type of vitamin D given.

## METHODS

### Types of studies

We will include randomised controlled trials of vitamin D supplementation with one of the following: placebo, no control or comparative arm studies. Comparative arm is an arm type in which a group of participants receives another dose of vitamin D, or fortified foods with vitamin D, or other micronutrients such as vitamin E during the clinical trial. Also, all the included studies must have reported 25(OH)D levels at baseline and at the end of the study.

### Types of participants

The participants are healthy children and adolescents (aged  $\leq 18$  years old) given vitamin D as a preventive measure of certain diseases or individuals with mild diseases (such as influenza, obesity, asthma, hypertension and so on) that have no reason to have altered vitamin D metabolism.

### Exclusion criteria

- ▶ Rickets in children characterised by low 25(OH)D (below 15 ng/mL) with radiological or laboratory evidence requiring higher doses of vitamin D supplementation (higher than those recommended for the general population).
- ▶ Individuals with chronic illnesses (chronic kidney disease (glomerular filtration rate at or below 30 mL/min), liver disease and heart failure (New York Heart Association class 3 or more)).
- ▶ Individuals with conditions or on drug therapy, both of which may affect vitamin D metabolism and vitamin D binding protein/metabolism (anticonvulsants, steroids, antifungal, malabsorption and bypass surgery).

### Types of intervention

#### Inclusion criteria

- ▶ Vitamin D (D<sub>2</sub> or D<sub>3</sub>) supplementation of any dose, given orally, daily, weekly or monthly, with or without calcium supplementation.

#### Exclusion criteria

- ▶ Studies that used active vitamin D supplementation (1,25-dihydroxyvitamin D) as this type of supplementation is not recommended for the general population.
- ▶ Studies that used vitamin D supplementation given intramuscularly.
- ▶ Studies that used vitamin D supplementation as fortified foods as the amount of vitamin cannot be defined accurately.

### Patient and public involvement

Patients and/or the public are not involved in this study.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

### Electronic searches

We will perform a systematic search of published randomised trials on vitamin D supplementation in

subjects aged  $\leq 18$  years in PubMed, Scopus, ISI Web of Science and Cochrane Central Register of Controlled Trials databases up to 27 September 2017, using eligible keywords in titles or abstracts (for details on search strategies, see online supplementary file 1), using the following search terms: (Vitamin D or ergocalciferol or cholecalciferol or calcidiol or calcitriol) and (25-hydroxyvitamin D or hydroxyvitamin D or 25OHD or 25(OH)D or 25-OH-vitamin D or hydroxycholecalciferol or 25-hydroxy vitamin D or hydroxyergocalciferol) and (clinical trial or controlled trial). Inclusion criteria will be  $\leq 18$  years (children and adolescents age group). The first search will be done without language restrictions using various combinations of relevant keywords. We will also perform a complete updated search on all databases available and identify new studies (if any exist) for inclusion, assess them and incorporate the findings in our review.

### Searching other resources

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

## DATA COLLECTION AND ANALYSIS

### Selection of studies

Two authors (GA, HF) will independently determine studies that should be evaluated further by scanning the title, abstract or both of every study retrieved based on the 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 to resolve differences and reach consensus (FH). Also, an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram will be presented to indicate the process of study selection.<sup>25</sup>

### Data extraction and management

In the first step, two authors (GA, HF) will independently select articles by title and abstract or search the reference lists of relevant studies, and in the second step full texts of selected articles will be retrieved and screened using the inclusion and exclusion criteria (study design, participants and intervention). Finally, in the third step, we will extract the relevant data from the selected articles in a structured data bank (GA, HF). We will resolve any disagreement through consensus or consultation with a third author to resolve differences (FH).

### 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 data set aggregated across all known publications.

### Quality assessment

The quality of each included study will be assessed independently by two authors (GA, HF). We will assess the quality assessment, focusing on the following criteria:

randomisation, allocation concealment, blinding of personnel and of participants, incomplete outcome data, selective reporting and other potential sources of bias using the Jadad scale.<sup>26</sup> We will resolve disagreements in quality assessments by consensus or by consultation with a third author (FH).

### Data synthesis

We will present the data of all included studies and provide a description of the results, including study population, intervention and outcome in detail in both summary tables and the text. Also, a meta-analysis using fixed-effects or random-effects modelling will be conducted to summarise the weighted mean differences and 95% CI in 25(OH)D from baseline to follow-up during the supplementation.<sup>27 28</sup> We will first perform graphical exploration of the variability of changes in 25(OH)D levels due to vitamin D doses. A potential non-linear or linear dose-response relationship between vitamin D supplementation and serum 25(OH)D concentration will be modelled using restricted cubic splines. We will fit meta-regression models for prediction of linear change in 25(OH)D concentration. We will complete statistical analyses based on the statistical guidelines contained in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions.<sup>29</sup>

If faced with any missing data in some studies in the process of analysis and data extraction and if we have proper evidence that indicates the randomness of these missing data, we will use data from existing data analyses; otherwise, we will obtain the missing data from the study authors if possible; an alternate method where the value of some indices, including mean or SD, is not reported for outcomes is to impute these values by assuming the mean and SD of the missing data to be the average of the mean or SD of the data from those studies where this information was given. To investigate the impact of imputation on meta-analyses, we will use sensitivity analysis.

### Assessment of heterogeneity

Any clinical, methodological or statistical heterogeneity of the data will be investigated via visual inspection of the forest plots and using  $X^2$  test with  $N-1$  df and significance level of  $\alpha=0.1$ . If the power of this test is low, we will also calculate heterogeneity by  $I^2$ , a transformation of the square root of the  $\chi^2$  test divided by its df.<sup>30</sup> If the values of  $I^2$  is high, we will have greater heterogeneity<sup>31</sup>; should there be heterogeneity in our investigation, we will assess the individual study and subgroup characteristics and perform a sensitivity analysis to clarify the reasons for this heterogeneity.<sup>32</sup>

### Assessment of publication biases

Publication bias will be assessed using funnel plot and statistical analysis of Egger's test.<sup>33 34</sup> We will only test for funnel plot asymmetry if our review includes over 10 studies that assess a specific outcome.



### Subgroup analysis

After the final search and screening, if a sufficient number of studies are available, we will perform subgroup analyses and investigate interactions based on the following: characteristics of participants, intervention, and outcomes including sex, 25(OH)D baseline level, puberty status, season, latitude, type of vitamin D, calcium supplementation, compliance, length of intervention, frequency of intervention, doses of vitamin D supplementation and quality of studies.

### Sensitivity analysis

We will carry out sensitivity analyses to explore the influence of the following factors on the effect sizes and validity of the estimations:

1. Investigation of the impact of quality assessment on the results.
2. An analysis of the influence of various characteristics of studies using the following filters: duration of intervention, sex, language of publication, country and dose of administration.
3. An assessment of the effect of different variance imputations.

### 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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**Contributors** GA had the original idea of this work. GA, HF and FH designed and conceived the protocol. NM designed the search strategies. PM proposed some important advice for the study design and revision, and PM and FA aided in developing the research questions. All authors critically revised the draft of the manuscript and approved its final version. GA and HF are the guarantors of the review.

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