Oct 18, 2022

Health Effects of Vitamin D: Evidence from Mendelian Randomization studies

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dx.doi.org/10.17504/protocols.io.eq2ly7nzmlx9/v1

Health Effects of Vitamin D Evidence from Mendelian Randomization studies

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ABSTRACT

Preclinical data and observational studies suggest that vitamin D has wide-ranging skeletal and extra-skeletal effects. However, it remains controversial whether the link between vitamin D and many health outcomes is causal or not. Mendelian randomization (MR) provides an alternative approach to facilitate causal inference in an observational setting. Here, we will systematically summarize and evaluate the evidence on vitamin D and various health outcomes from MR studies.

DOI

dx.doi.org/10.17504/protocols.io.eq2ly7nzmlx9/v1

PROTOCOL CITATION

Aiping Fang, Yue Zhao, Ping, Xuehong, Edward Gio 2022. Health Effects of Vitamin D: Evidence from Mendelian Randomization studies. **protocols.io** https://dx.doi.org/10.17504/protocols.io.eq2ly7nzmlx9/v1

CREATED

Oct 17, 2022

LAST MODIFIED

Oct 18, 2022

PROTOCOL INTEGER ID

71447

Background

1 There is an ongoing debate about the skeletal and extraskeletal effects of vitamin D. A large number of epidemiological studies have been conducted but yield conflicting results[1]. Although randomized controlled trials (RCTs) are considered the gold standard to identify causality, a large RCT with disease outcomes is usually expensive, time-consuming, and even practically or ethically unfeasible. Mendelian randomization (MR) studies provide an alternative approach to facilitate causal inference on vitamin D-disease associations in a cost-effective and timely manner by using genetic variants as proxies for vitamin D status.[2]

2 In the last decade, MR analyses have attracted great research interest with the growing availability of genomic information from large-scale genome-wide association studies (GWAS). A wealth of MR studies has investigated the association of genetically predisposed serum 25(OH)D concentrations with various health outcomes, such as musculoskeletal diseases, allergic and autoimmune diseases, cardiovascular diseases (CVDs), cancer incidence and survival, neuropsychological disorders, metabolic diseases, and infectious diseases, as well as all-cause and cause-specific mortality. Summarizing the available evidence will provide a bird's view of the most promising area of vitamin D intervention in public health nutrition.

Aim of the study

3 1) To provide an overview of the current evidence on the causal association between vitamin D and multiple health outcomes in an MR framework;
2) To perform meta-analyses to synthesize relevant evidence after excluding overlapping study populations, if possible;
3) To systematically assess the methodological quality of the available MR studies.

Data sources and search strategy

4 PubMed and Embase will be searched for published, peer-reviewed MR studies using GIs as a proxy for vitamin D status in relation to any health outcome.

The search syntaxes are listed as follows:
PubMed:
((((("Vitamin D"[Mesh]) OR (vitamin D[Title/Abstract])) OR (("25-Hydroxyvitamin D 2"[Mesh] OR "Calcifediol"[Mesh] OR "25-hydroxyvitamin D" [Supplementary Concept]) OR (((25-Hydroxyvitamin D[Title/Abstract]) OR (25-hydroxy-vitamin D[Title/Abstract])) OR (25OHD[Title/Abstract] OR 25(OH)D[Title/Abstract] OR 25-OHD[Title/Abstract])))) AND (("Mendelian Randomization Analysis"[Mesh]) OR ((Mendelian randomisation[Title/Abstract]) OR (Mendelian Randomization[Title/Abstract]))))

Embase:
Sources: Embase, Embase Classic, MEDLINE, Preprints
Query: ('vitamin d'/exp OR 'vitamin d':ab,ti OR '25 hydroxyvitamin d'/exp OR '25 hydroxyvitamin

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d':ab,ti OR calcifediol:ab,ti OR '25-hydroxy-vitamin d':ab,ti OR 25ohd:ab,ti OR '25 ohd':ab,ti OR (25:ab,ti AND oh:ab,ti AND d:ab,ti)) AND ('mendelian randomization analysis'/exp OR 'mendelian randomization':ab,ti OR 'mendelian randomisation':ab,ti)

We will also manually screen the reference lists of relevant reviews and the included studies to identify additional studies.

Eligibility criteria and study selection

5 Exclusion criteria:
1) duplicate publications;
2) non-original studies, e.g., reviews, conference abstracts, editorials, commentaries, correspondences, opinions, corrections, and study proposals;
3) methodological studies that used vitamin D only as an example of the application of MR;
4) studies that used vitamin D status as an outcome;
5) studies that did not provide sufficient original data, i.e., effect size and 95% confidence intervals (CIs) or standard error (SE) for the studied association;
6) studies that only reported single variant–outcome associations;
7) studies only using variants in the vitamin D-binding protein gene as instrumental variables (e.g., rs2282679, rs7041 in the GC gene);
8) studies that only employed biomarkers or surrogate endpoints (e.g., serum lipids, bone mineral density) as outcomes.

Two reviewers will independently screen the titles and abstracts of all retrieved studies and subsequently review the full text of potentially eligible studies in Covidence software. Any discrepancy was resolved by discussion.

Data extraction

6 Baseline study characteristics will be extracted
- Title, first author, year of publication, MR design (one-sample/two-sample), exposure(s) and outcome(s).

For the genetic instrument(s) used in each study, the following information will be extracted:
- Gene name
- Number of SNPs
- Specific SNPs
- Type of the genetic instrument(s)
- Proportion of variance explained by the genetic instruments
- F-statistic
- *P*-value threshold for SNP selection
- Threshold for SNP linkage disequilibrium (r^2)
- Biological relevance
- Statistical power of the genetic instruments and the corresponding effect estimate

For the exposure(s) and outcome(s) of each study, the following information will be extracted:
- Data source and ancestry
- Sample size (total participants, cases, controls)

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- Covariates adjusted in the analysis

For the result(s) of each study, the following information will be extracted:
- Type of instrumental variable (IV) analysis (formal or reduced IV)
- Unit of estimated effect
- Analytical approach for main analysis
- Effect metric, effect size and the corresponding 95% CIs, as well as *P*-value
- Cochran's Q-statistic and I-square statistic (I^2) for heterogeneity
- Sensitivity analysis methods and results, if applicable

Quality assessment

7 A scoring system was developed to assess the methodological quality of the included studies according to the published guidelines[3-6]. The scoring system has 11 items, including the type of IV analysis, three core IV assumptions (relevance assumption, independence assumption, exclusion-restriction assumption), population heterogeneity, GI selection, MR results reporting, sensitivity analysis (whether sensitivity analyses were preformed, and whether the results from the sensitivity analyses were consistent with those from the main analysis), and dose-response relationship (linearity, nonlinearity).

Data analysis

8 Qualitative analysis:
Selected data will be summarized according to baseline study characteristics and significance of the results.

Quantitative analysis:
After excluding overlapping outcome samples, we will perform quantitative analysis. For studies which presented standard errors, values will be converted to 95% CI. Units will be standardized to common units. If MR estimates were presented for an identical outcome based on two or more non-overlapping study populations on the same scale, we will further conduct meta-analyses to combine the estimates. The heterogeneity among studies was quantified with the I^2 statistic. I^2>50%) was considered high heterogeneity, in which case a random-effects model was used; if not, a fixed-effect model was adopted. Meta-analyses were performed using the 'meta' package, and forest plots were generated using the 'forestplot' package (R software version 4.1.1). A two-tailed P value < 0.05 was considered statistically significant.

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