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The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis

An OA Trial Bank protocol for a systematic review and individual patient data meta-analysis

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Keywords

Systematic Review; Meta-analysis; Individual Patient Data; Osteoarthritis; Vitamin D; Knee.

Abstract

Introduction

Observational data suggest vitamin D deficiency is associated with the onset and progression of knee osteoarthritis (OA). Vitamin D supplementation may be a promising cost-effective treatment. However, randomized clinical trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Recent systematic reviews with aggregate data from these RCTs suggest that further research is needed to clarify the effects on patient-reported outcomes and determine whether there are OA patient subgroups who may benefit from vitamin D. The aim of this study is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function. A systematic literature search will be conducted for RCTs comparing vitamin D supplementation with other control treatments in individuals with knee OA. Authors of original trials will be contacted to obtain individual patient data (IPD) from each study.

Methods and analysis

The primary outcomes will include long-term ($\geqslant$ 12 months) pain and physical function. Secondary outcomes will include medium-term ($\geqslant$6 months and <12 months) and short-term (<6 months) pain and physical function, as well as patient global assessment and quality of life. Potential treatment effect modifiers to be examined in the subgroup analyses include age, gender, body mass index, baseline knee pain severity and physical function, baseline vitamin D level, radiographic stage, presence of bone marrow lesions on MRI, presence of clinical signs of local inflammation, and concomitant depressive symptoms. Both one-step and two-step modelling methods will be used to determine the possible modifiable effect of each subgroup of interest.

Discussion

This study will be the first meta-analysis of vitamin D supplementation for knee OA using IPD from RCTs. This study will clarify the effect of vitamin D supplementation on clinical symptoms in different subgroups of patients with knee OA.

Systematic review registration

This systematic review is registered on PROSPERO (CRD42018107740).

Article Summary

This article is a protocol for a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation on joint pain and physical function in patients with symptomatic knee OA.

Strengths and limitations of this study

- This study protocol is endorsed by the OA Trial Bank, an international collaboration that initiates meta-analyses on predefined subgroups of OA patients.
- This study is the first IPD meta-analysis to identify OA patient subgroups that may benefit from vitamin D supplementation.
- IPD meta-analysis offer greater statistical power and precision than subgroup analysis in a single trial and conventional meta-analysis using aggregate data.
- Analysis may be limited to the variables that have been collected across included RCTs.

Introduction

Osteoarthritis (OA) is the most common joint disorder worldwide. OA is ranked as the 13th highest contributor of 310 diseases to global disability in 2015[1]. In Australia, OA affects over 2.1 million people (9% of the population), costing the healthcare system over $2.1 billion in 2015[2]. This cost is forecasted to increase by 41% in 2030[3].

Knee OA accounts for 83% of the disease burden of OA[4] and is characterized by pain, gradual loss of articular cartilage, and structural changes such as subchondral remodelling and effusion-synovitis[5]. Currently, there are no effective disease-modifying treatments to reverse the progression of knee OA once the disease is established. A majority of patients with knee OA eventually progress to advanced stage and undergo total knee replacement[6]. There is clearly an urgent need for innovative and cost-effective approaches to slow the progression of knee OA.

Emerging observational data suggest that vitamin D insufficiency is associated with the onset and progression of knee OA[7]. The association between low serum vitamin D levels and knee OA symptoms may be explained by a direct effect of vitamin D on chondrocytes in osteoarthritic cartilage[8], as well as indirect effects on subchondral bone, synovium, and periarticular muscle[9]. For example, vitamin D deficiency could impair the ability of bone to respond optimally to pathological bone marrow lesions (BMLs) and altered bone mineral density, therefore predisposing the knees to disease progression[10]. Vitamin D also may reduce synovitis in affected knees by regulating cytokine levels in the joint, leading to a reduction in the amount of effusion-synovitis in magnetic resonance images (MRI)[11]. In addition, depressive symptoms is interrelated to joint pain in OA[12], and maintaining sufficient serum vitamin D may improve depression symptoms in patients with knee OA[13].

However, evidence from randomized controlled trials (RCTs) have been conflicting[14–17]. A pilot RCT in India found a small but statistically significant clinical benefit for 12-month vitamin D treatment on pain and function in patients with knee OA, compared with placebo[16]. In contrast, a subsequent RCT from the US showed that vitamin D supplementation did not reduce knee pain or cartilage volume loss over 24 months[15]. Subsequently, data from RCTs in Australia[17] and UK[14] did not find significant clinical benefits of vitamin D supplementation for knee OA. However, a there was a non-significant trend of symptom reduction (e.g. knee pain and physical function) in these RCTs. Two systematic reviews of aggregate data from these RCTs concluded that, although current evidence does not support vitamin D supplementation for reducing structural disease progression, further research is needed to clarify the effects on patient-reported outcomes[18,19].

The null results of these RCTs could be due to a low prevalence of vitamin D deficiency in the study subjects or low statistical power secondary to small sample sizes. Another possible reason is that vitamin D may have an effect only in some OA phenotypes, such as those with BMLs (predominant bone abnormality)[20], effusion-synovitis (inflammatory)[21] or depressive symptoms (psychological distress)[13]. Post hoc analyses within these RCTs were frequently underpowered, and hence unreliable to determine the effect of vitamin D treatment on subgroups of knee OA patients. A meta-analysis using individual patient data (IPD) can increase the power by combining individual trials[22] and hence can quantify the vitamin D treatment effects in these subgroups.

Methods and analysis

We will conduct a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation in patients with symptomatic knee OA. The primary aim is to identify patient-level predictors of treatment response to vitamin D supplementation, including the status of vitamin D deficiency, MRI-detected bone marrow abnormalities and effusion-synovitis, and clinical signs of local inflammation. The protocol of this review is registered on the PROSPERO database (CRD42018107740).

Literature search

A systematic literature search for articles published from January 1990 until November 2019 will be performed in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE;

The search strategies used for each database are listed in *Appendix 1*. All retrieved articles will be exported to the reference manager *EndNote,* in which duplicates will be removed. The remaining records will be exported to an online systematic review management tool *Covidence* (Veritas Health Innovation, Melbourne, Australia) and the articles will be assessed for eligibility for inclusion. In addition to the electronic search, we will check the reference lists of included trials and previous systematic reviews to identify any trials that are not retrieved from the electronic search. Review authors and collaborating authors will be asked if they are aware of further relevant studies not yet included. We will also search the WHO International Clinical Trial Registration Platform Search Portal (www.who.int/trialsearch) to identify any relevant trials that are completed but did not published the results.

Study selection

Two review authors (XJ, BA) will independently conduct study screening by assessing the article titles and abstracts. Full texts of the articles will be further assessed if the information from the abstract suggests that a study is eligible for inclusion. When information contained in the full text is not sufficient to make a judgement on its eligibility, we will make efforts to contact the corresponding authors to obtain further details. If a corresponding author is not contactable after two email attempts and one phone call, the study will be deemed ineligible. Any disagreement regarding the inclusion of a study will be discussed between the two review authors (XJ, BA). If no consensus can be reached, a third review author will be consulted (XW) to make a final decision.

Type of studies

Published RCTs that reported the efficacy of vitamin D in participants with knee OA will be included. Cross-over design will also be eligible and only the first phase data will be included in the analysis. Both open-labelled and blinded studies will be eligible. There will be no language or geographical restrictions applied to study selection.

Participants

Men and women who have a diagnosis of knee OA, either according to the American College of Rheumatology criteria, or on the basis of detailed clinical and/or radiographic information, will be included. Studies with a subgroup of knee OA patients will also be included, provided that IPD can be collected separately for the OA subgroup.

Interventions

Only studies investigating oral supplementation of vitamin D will be included. Vitamin D treatments administered subcutaneously, intraperitoneally or intravenously will not be included. Both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) will be eligible, irrespective of preparations (tablet or capsule), dosage, regimen, and length of treatment.

Comparators

Oral vitamin D supplementation will be compared with control treatment including placebo or usual conservative care (pain medication and/or exercise therapy if they are used in both treatment and control groups).

Outcomes

The minimum criterion for inclusion of trial in the systematic review is reporting pain or physical function as either primary or secondary outcomes. There will be no restrictions on the

duration of follow-up. Data on other outcomes (e.g. patient's global assessment, quality of life, and adverse events) will be analysed when feasible but will not be required for study selection.

Baseline assessments

As a minimum, included studies should have measured knee pain, physical function, serum levels of vitamin D, and basic patient characteristics including age, gender, and body mass index (BMI) at baseline.

Extraction of aggregate data

Study data extraction will be performed independently by two review authors (BA, XW). Discrepancies will be resolved by a third reviewer (XJ). We will extract the following study data from the included studies:

- General information: article title, bibliographic details, published language, and funding source.
- Participants: inclusion criteria, exclusion criteria, number of participants in total and in each study arm, study settings, and baseline participant characteristics (e.g. age, gender, BMI).
- Intervention: type of vitamin D preparation, dose, regimen, treatment duration, type of control, and co-interventions (if any).
- Outcomes: primary and secondary outcomes at the end of treatment and/or the end of follow-up. Number of withdrawals and loss to follow-up. Adverse events recorded.
- Data analysis: statistical models used for data analysis, confounding factors adjusted in the models, and methods used for addressing missing values.

Risk of bias assessment

The methodological quality of the included studies will be assessed using a modified version of the Cochrane's risk of bias tool[23]. The modified version includes all the seven domains of the original tool, but further separates performance bias assessment into 'blinding of participants' and 'blinding of study personnel', as well as pre-specifies other sources of bias as 'balance in baseline covariates', 'treatment compliance', and 'timely outcome assessment' (*Table 1*). Each domain will be scored as 'low risk', 'high risk' or 'unclear' according to the criteria described in the *Appendix 2*. The overall rating of study quality is based on the number of domains with a 'high-risk' score. The overall rating is intended to inform readers of the study quality and will not be used to weight the studies in the meta-analysis. Two review authors (XJ, XW) will independently evaluate the quality of an individual study. Any

disagreement will be settled by further discussion until a consensus is reached between the two review authors.

IPD collection and transfer

The primary or corresponding authors of included trials will be invited to collaborate on the project and contribute their raw data. When we cannot reach a corresponding author after sending two emails and making two telephone calls, we will contact the co-authors listed in the article. If none of the co-author can be contacted, we will approach the institutes, in which the trial has been conducted. All data custodians will be asked to sign a data delivery agreement, which includes items regarding IPD delivery, obligations, ownership of data, terms and conditions of the use of the data, authorship, and publications. If needed, the project coordinator (XJ) will visit the institutes of the data deliverers to retrieve the data and to sign the data delivery agreement on behalf of the OA Trial Bank. De-identified datasets will be accepted in any electronic format (for example, SPSS, Stata, SAS, Excel) or in paper form, provided that variables and categories are adequately labelled within the dataset or within a separate codebook. The IPD files received by the coordinator will be kept in their original version and saved on a secured password-protected server at Erasmus MC Medical University in Rotterdam. The datasets will not be used for any other research apart from that described in the license agreement.

To ensure the quality of the data, the coordinator will independently check for data consistency by comparing the summary statistics derived from the IPD received against the summary results reported in the published articles. In the case of differences, the project coordinator will communicate with the data deliverer via email or teleconference to resolve the discrepancy.

Variables of interest

The following IPD variables will be obtained (where available):

Primary outcome variables

The primary outcomes for this meta-analysis will be pain and physical function at long-term follow-up (12 months or more).

- Knee pain will be evaluated using visual analogue scale (VAS) if available, otherwise the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[24] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[25] will be used. The pain data will be converted into a 0-100 common scale as recommended by the WOMAC manual[26].

- Physical function will be evaluated using a validated instrument specific to knee OA, such as the physical function subscales of the WOMAC or the KOOS subscales. The scores will be standardised into a 0-100 scale.

Secondary outcome variables

Secondary outcomes will include:

- Medium-term (more than 6 months but less than 12 months) pain and physical function;
- Short-term (less than 6 months) pain and physical function;
- Patient global assessment at the end of study follow-up, as recommended by the OMERACT-OARSI Initiative[27].
- Quality of life evaluated using a validated instrument, such as EQ-5D[28], osteoarthritis Knee and Hip Quality of Life (OAKHQOL)[29], or original instrument used in the included studies;
- Adverse events if reported, including all major and minor events such as hypocalcaemia, fractures, and depression.

Potential treatment effect moderators

If data are available, we will analyse potential treatment effect modification for the following variables measured at baseline:

- Radiographic stage of knee OA (mild/moderate or severe). Radiographic knee OA should be staged at baseline using either the Kellgren-Lawrence (KL)[30] or Osteoarthritis Research Society International (OARSI) joint space narrowing (JSN) grading system[31]. The results from the two grading systems have been shown to be highly correlated[32]. Mild to moderate disease will be defined as a KL score ≤ 3 or an OARSI JSN score ≤ 2, and severe disease will be a KL score of 4, or an OARSI score of 3.
- Vitamin D level (deficiency, insufficiency, or sufficiency). Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥50 nmol/L is considered as vitamin D sufficiency[33].
- Presence of BMLs (yes or no). BMLs at the patella-femoral and femoro-tibial joints should be measured by MRI using a validated scoring system, such as BLOKS (Boston Leeds Osteoarthritis Knee Score)[34], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[35], or KOSS (Knee Osteoarthritis Scoring System)[36].

- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination - tumor (swelling), dolor (pain), rubor (redness), calor (heat), and functio laesa (disturbance of function) - or by additional laboratory testing (e.g. serum c-reactive protein and erythrocyte sedimentation rate). Effusion-synovitis should be measured on either ultrasound or MRI.
- Presence of depressive symptoms or comorbid depression. Depressive symptoms are measured using a validated questionnaire, such as the Patient Health Questionnaire (PHQ-9)[37] and the Geriatric Depression Scale (GDS)[38].

Statistical analysis

All statistical analysis will be conducted in R version 3.3.2 and RStudio (version 1.0.136, RStudio, Inc., Boston, MA).

Conventional meta-analysis

An aggregate data meta-analysis, using a random-effects model, will be performed to estimate the treatment effect of vitamin D over control. The results will be compared with the IPD meta-analysis findings as sensitivity analyses.

Heterogeneity will be assessed by inspecting the forest plots. In addition, heterogeneity will be tested by both Chi^2 test and I^2 test. A result of $Chi^2 > 25\%$ and $p < 0.10$ will be defined as evidence of significant heterogeneity across studies. I^2 test will be used to estimate the extent of variability across studies that is due to heterogeneity. A result of over 30% and 50% represents moderate and substantial heterogeneity, respectively. Sources of heterogeneity will be explored by excluding individual trials causing an I^2 score below 50%.

If 10 trials or more trials are available[39], funnel plots of treatment effect against its standard error will be used to explore publication bias and 'small-study effects'. Asymmetry in the funnel plots will imply possible small-study effects. A modified 'Egger' regression test will be conducted to detect such asymmetry. $P < 0.10$ will be deemed to have considerable small-study effects.

IPD meta-analysis

IPD from included trials will be recoded and formatted in a consistent way to permit re-analysis. A new variable will be created to indicate the trial in which the IPD are collected. The method used to handle missing data will depend on the mechanism causing the missingness. If no explanation is known for the reason of missing data, they will be assumed to be missing at random. We will use the R MICE package[40] for multiple imputation and the

imputation model will include all available patient variables to help predict missing data for the variables of interest within each study dataset. The imputation procedure will use 20 imputed datasets. A sensitivity analyses will be performed restricting to participants without missing data (complete case analysis).

Both the treatment effect of vitamin D supplementation and the effect of potential moderators will be studied in the IPD meta-analyses. The treatment effect of vitamin D will be measured using the mean difference in knee pain and physical function between treatment and control based on the intention-to-treat principle. The interaction between the treatment and a potential moderator will be used to identify the effect of the moderator. Interaction effects with $P < 0.05$ will be considered statistically significant. The IPD meta-analyses will be undertaken using both the one-stage and two-stage approaches. We will use the one-stage approach as the primary analysis to avoid assumption of within-study normality and known within-study variance[41]. We will and compare the results to the two-stage approach to assess consistency in a sensitivity analysis.

One-stage modelling

The one-stage mixed-effects IPD meta-analysis approach will take into account both study level and subject-level covariates. Subject -level covariates will be centred to the mean of the covariate in each trial to avoid ecological bias. Two multilevel regression models will be built, one to examine the summary treatment effect (difference between vitamin D and control) and the other to evaluate different moderators on treatment effect.

The first model will include outcome measure (e.g. pain score at follow-up) as a dependent variable, treatment (vitamin D or control), baseline subject-level covariate (e.g. pain score) and confounders (age, gender and BMI) as fixed-effect independent variables, adjusted for study identifier (random intercept). The partial regression coefficient of the treatment will be used to compare to the conventional meta-analysis.

The second model will further add the moderator of interest (e.g. radiographic stage of the disease) and interaction term between the treatment and study-centred values of the moderator in the fixed-effect of the first model. The regression coefficient of the interaction term will be used to quantify the impact of the moderator on treatment effect.

Two-stage modelling

In the first stage, treatment effect and variance are derived from separate analysis in each study. An analysis of covariance (ANCOVA) model adjusted for baseline covariates (age, gender,

BMI, as well as knee pain or function), will be used to obtain the treatment effect and variance within each study separately. The effect of a moderator and its variance within each study will be obtained by adding the interaction term between treatment effect and the moderator into the model. In the second stage, the treatment effect and its variances obtained from the first stage will be pooled across studies using a fixed-effect model based on the inverse-variance approach. The result of this model is a summary estimate of the treatment effect of vitamin D versus control. The effect of a moderator will be calculated by pooling the regression coefficient and variance of the interaction term between the treatment and the moderator using a similar model.

Discussion

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial[7,18]. In a few existing RCTs in patients with symptomatic knee OA[27,14,16,17], small to modest improvement in knee pain and physical function were observed in participants receiving vitamin D supplementation, but the treatment response varies considerably and the effects were not statistically significant when compared to placebo. The broad variation in treatment response could be a result of the fact that knee OA is a highly heterogenous disease with multiple aetiologies. Vitamin D may therefore be more effective in a subset of patients with specific characteristics than others. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short- and long-term follow-up.

An IPD meta-analysis is an integrated part of precision medicine[42]. It is a cost-effective approach to identify potential moderators of treatment response at a patient level, which is not possible with subgroup analyses in a single trial or conventional meta-analysis with aggregate data. Subgroup analyses within individual trials are often underpowered to generate reliable findings. In contrast, IPD meta-analysis techniques increase the statistical power of the study by combining multiple trials with the same treatment. This offers greater precision in analysing moderators of treatment response and offers the potential to analyse a greater number of moderators. In conventional meta-analysis, meta-regression analysis may be used to examine differences in the types of patients enrolled in individual trials, but is potentially problematic. Meta-regression analysis may make incorrect inferences about individual characteristics based upon aggregate baseline statistics reported in trial publications. This is also known as

ecological fallacy, where the relationship between the effect estimate and average patient characteristics across trials may not be the same as the relationship within individual trials.

Identifying different phenotypes of knee OA is currently a popular subject of research in the field. Different phenotyping strategies have been proposed based on risk factors from epidemiological studies[43], anatomical abnormalities on modern imaging[44], or molecular abnormalities related to pathological mechanisms[45]. While there is currently no standardised classification system for knee OA phenotypes[5], we believe that disease phenotypes are most meaningful when they reflect differential treatment effects. IPD meta-analysis provides an opportunity to assess the effect of treatments on subtypes or phenotypes of patients with knee OA according to predefined set of characteristics. The current proposed IPD meta-analysis attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

Strengths and limitations

Several challenges may present when conducting an IPD meta-analysis. First, although IPD meta-analyses usually offer sufficient statistical power to examine moderators of treatment response, not all RCTs measure potential moderators of interest or measure them in the same way. This may limit the analysis to only exploring moderators that have been collected across studies. The current protocol attempts to minimise this risk by including moderators that are commonly reported in OA research. In addition, there are expected barriers to accessing data, such as the authors of included trials not being able to be contacted, or the authors losing access to raw data or not choosing to collaborate, may introduce selection bias into the IPD meta-analysis. However, this will be examined in sensitivity analyses by comparing the results to the conventional meta-analysis.

The benefits of using IPD meta-analysis techniques greatly outweigh the challenges of using this intensive method. Previous RCTs and systematic reviews have not had sufficient power to thoroughly examine the differential treatment response of vitamin D supplementation in different subsets of patients with knee OA.

The results of this project have a high potential to provide important evidence to guide subgroup-specific treatment decisions in clinical practice to improve therapeutic effectiveness.

Status of project

Currently, literature search in the electronic databases has been commenced.

Abbreviations

OA: osteoarthritis; IPD: individual patient data; RCT: randomised controlled trial; BMI: body mass index; MRI: magnetic resonance imaging; BMLs: bone marrow lesions; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International.

Additional Information

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We acknowledge the University of Sydney China Study Centre for providing short-term travel support to establish international collaboration for this project.

Ethics approval and consent to participate

Research ethical or governance approval is exempt for this study as no new data are being collected.

Consent for publication

All authors have given consent for publication of the manuscript.

Availability of data and material

Not applicable.

Authors contributions

All authors were involved in the study design and all will contribute to the interpretation of the results. CD, BA and XJ concepted this study. WZ and MP provided methodological support for statistical analysis. XJ and BA will contact the potential data delivers and will coordinate the project. CD, TM, NA and RNS will deliver relevant data from their completed trials. SBZ and MM will facilitate legal agreement for data transfer and provide database management at the OA Trial Bank. XJ, BA and XW will perform the study selection, risk of bias assessment, data collection and analysis. All authors contributed to writing of this manuscript and approved the final submission.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and public involvement

We do not directly include patient and public involvement in this study, but the design of included randomised controlled trials may involve patients.

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Table 1. Modified risk of bias assessment

Source of bias[#]	Low risk	High risk	Unclear	Comments
1. Random sequence generation	☐	☐	☐	
2. Allocation concealment	☐	☐	☐	
3. Blinding of participants	☐	☐	☐	
4. Blinding of key study personnel	☐	☐	☐	
5. Blinding of outcome assessment	☐	☐	☐	
6. Incomplete outcome data	☐	☐	☐	
7. Selective outcome reporting	☐	☐	☐	
8. Imbalance in baseline covariates	☐	☐	☐	
9. Treatment compliance	☐	☐	☐	
10. Timing of outcome assessment	☐	☐	☐	
Overall risk of bias	**Low**	**Moderate**	**High**	
	☐	☐	☐	

[#]See *Appendix 2* for criteria for different levels of risk.

Appendix 1. Search strategy

Cochrane CENTRAL

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab,kw

#3. (degenerative near/2 arthritis):ti,ab,kw

#4. coxarthrosis:ti,ab,kw

#5. (#1 OR #2 OR #3 OR #4)

#6. MeSH desclriptor vitamin D explode all trees

#7. (vitamin D):ti,ab,kw

#8. (vitamin D2):ti,ab,kw

#9. (vitamin D3):ti,ab,kw

#10. (1-alpha hydroxyvitamin D3):ti,ab,kw

#11. (1-alpha-hydroxy-vitamin D3):ti,ab,kw

#12. (1-alpha hydroxycalciferol):ti,ab,kw

#13. (1-alpha-hydroxy-calciferol):ti,ab,kw

#14. (1,25 dihydroxyvitamin D3):ti,ab,kw

#15. (1,25-dihydroxy-vitamin D3):ti,ab,kw

#16. (1,25 dihydroxycholecalciferol):ti,ab,kw

#17. (1,25-dihydroxycholecalciferol):ti,ab,kw

#18. (25-hydroxycholecalciferol):ti,ab,kw

#19. (25 hydroxycholecalciferol):ti,ab,kw

#20. (25 hydroxyvitamin D):ti,ab,kw

#21. (25-hydroxy-vitamin D):ti,ab,kw

#22. (alfacalcidol):ti,ab,kw

#23. (calcidiol):ti,ab,kw

#24. (calcitriol):ti,ab,kw

#25. (calcifediol):ti,ab,kw

#26. (calciferol):ti,ab,kw

#27. (ergocalciferol):ti,ab,kw

#28. (cholecalciferol):ti,ab,kw

#29. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)

#30. #5 AND #29

MEDLINE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials.sh.
33. random allocation.sh.
34. double blind method.sh.

35. single-blind method.sh.
36. clinical trial.pt.
37. clinical trials.sh.
38. clinical trial.tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
40. placebos.sh.
41. placebo$.tw.
42. random$.tw.
43. Research Design/
44. comparative study.sh.
45. evaluation studies.sh.
46. follow-up studies.sh.
47. prospective studies.sh.
48. control$.tw.
49. prospectiv$.tw.
50. volunteer$.tw.
51. or/30-50
52. (animal not human).mp.
53. 46 not 47
54. 5 and 29 and 53

EMBASE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. random$.tw.
31. factorial$.tw.
32. crossover$.tw.
33. cross over$.tw.
34. cross-over$.tw.

35. placebo$.tw.
36. (doubl$ adj blind$).tw.
37. (singl$ adj blind$).tw.
38. assign$.tw.
39. allocat$.tw.
40. volunteer$.tw.
41. Crossover Procedure/
42. double-blind procedure.tw.
43. Randomized Controlled Trial/
44. Single Blind Procedure/
45. or/30-44
46. (animal/ or nonhuman/) not human/
47. 45 not 46
48. 5 and 29 and 47

Appendix 2. Modified risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Sequence generation process involves judgement or some method of non-random categorisation of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of "High risk":

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2
Authors					
Contact	3a	Provide name, institutional affiliation, and 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 15
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	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 5
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	☒	☐	Page 5, Appendix 1.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8-10
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 8-9
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 7, Appendix 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-12
	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 (e.g., I^2, Kendall's tau)	☒	☐	Page 10-12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	N/A

BMJ Open

The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA) - An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035302.R1
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Date Submitted by the Author:	19-Dec-2019
Complete List of Authors:	Jin, Xingzhong; Southern Medical University, Zhujiang Hospital; The University of Sydney, The Boden Collaboration for Obesity, Nutrition, Exercise & Eating Disorders Antony, Benny; University of Tasmania, Menzies Institute for Medical Research Wang, Xia; The University of Sydney, Institute of Bone and Joint Research Persson, Monica; University of Nottingham Faculty of Medicine and Health Sciences McAlindon, Timothy; Tufts Medical Center, Arden, Nigel; Nuffield Department of Orthopaedics, ; Srivastava, Sudeepti; King George Medical College Srivastava, Rajeshwar; King George Medical University van Middelkoop, Marienke; Erasmus MC Bierma-Zeinstra, Sita; Erasmus MC Zhang, Weiya; University of Nottingham, Academic Rheumatology Cicuttini, Flavia; Monash University, Department of Epidemiology and Preventative Medicine Ding, Changhai; University of Tasmania, Menzies Institute for Medical Research
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Complementary medicine
Keywords:	PREVENTIVE MEDICINE, RHEUMATOLOGY, GENERAL MEDICINE (see Internal Medicine)

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The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA)

An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

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Keywords

Systematic Review; Meta-analysis; Individual Patient Data; Osteoarthritis; Vitamin D; Knee.

Abstract

Introduction

Observational data suggest vitamin D deficiency is associated with the onset and progression of knee OA. However, randomized controlled trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Further research is needed to clarify the effects of vitamin D on patient-reported outcomes and determine whether there are patient subgroups who may benefit from the supplementation. The aim of this IPD meta-analysis is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function.

Methods and analysis

A systematic literature search will be conducted for RCTs of vitamin D supplementation on knee OA. Authors of original RCTs will be contacted to obtain the IPD. The primary outcomes will include long-term ($\geqslant$12 months) pain and physical function. Secondary outcomes will include medium-term ($\geqslant$6 months and <12 months) and short-term (<6 months) pain and physical function, as well as patient global assessment, quality of life and adverse events. Potential treatment effect modifiers to be examined in the subgroup analyses include age, gender, body mass index (BMI), baseline knee pain severity and physical function, baseline vitamin D level, radiographic stage, presence of bone marrow lesions on magnetic resonance images (MRI), presence of clinical signs of local inflammation, and concomitant depressive symptoms. Both one-step and two-step modelling methods will be used to determine the possible modifiable effect of each subgroup of interest.

Ethics and dissemination

Separate ethics committee approval because this study involves analysis of de-identified data that have already been collected in individual RCTs. This study will be the first IPD meta-analysis to clarify the effect of vitamin D supplementation on clinical symptoms in different subgroups of patients with knee OA. The findings will be disseminated through peer-review publications and conference presentations.

Systematic review registration

This systematic review is registered on PROSPERO (CRD42018107740).

Article Summary

This article is a protocol for a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation on joint pain and physical function in patients with symptomatic knee OA.

Strengths and limitations of this study

- This study protocol is endorsed by the OA Trial Bank, an international collaboration that initiates meta-analyses on predefined subgroups of OA patients.
- This study is the first IPD meta-analysis to identify OA patient subgroups that may benefit from vitamin D supplementation.
- IPD meta-analysis offer greater statistical power and precision than subgroup analysis in a single trial and conventional meta-analysis using aggregate data.
- Analysis may be limited to the variables that have been collected across included RCTs.

Introduction

OA is the most common joint disorder worldwide. OA is ranked as the 13th highest contributor of 310 diseases to global disability in 2015[1]. In Australia, OA affects over 2.1 million people (9% of the population), costing the healthcare system over $2.1 billion in 2015[2]. This cost is forecasted to increase by 41% in 2030[3].

The majority (83%) of the disease burden of OA is attributable to knee OA[4], which is characterized by pain, gradual loss of articular cartilage, and structural changes such as subchondral remodelling and effusion-synovitis[5]. Currently, there are no effective disease-modifying treatments to reverse the progression of knee OA once the disease is established. A majority of patients with knee OA eventually progress to advanced stage and undergo total knee replacement[6]. There is clearly an urgent need for innovative and cost-effective approaches to slow the progression of knee OA.

Emerging observational data suggest that vitamin D insufficiency is associated with the onset and progression of knee OA[7]. The association between low serum vitamin D levels and knee OA symptoms may be explained by a direct effect of vitamin D on chondrocytes in osteoarthritic cartilage[8], as well as indirect effects on subchondral bone, synovium, and periarticular muscle[9]. For example, vitamin D deficiency could impair the ability of bone to respond optimally to pathological bone marrow lesions (BMLs) and altered bone mineral density, therefore predisposing the knees to disease progression[10]. Vitamin D also may reduce synovitis in affected knees by regulating cytokine levels in the joint, leading to a reduction in the amount of effusion-synovitis in MRI[11]. In addition, depressive symptoms is interrelated to joint pain in OA[12], and maintaining sufficient serum vitamin D may improve depression symptoms in patients with knee OA[13].

However, evidence from RCTs have been conflicting[14–17]. A pilot RCT in India found a small but statistically significant clinical benefit for 12-month vitamin D treatment on pain and function in patients with knee OA, compared with placebo[3916]. In contrast, a subsequent RCT from the US showed that vitamin D supplementation did not reduce knee pain or cartilage volume loss over 24 months[15]. Subsequently, data from RCTs in Australia[17] and UK[14] did not find significant clinical benefits of vitamin D supplementation for knee OA. However, there was a non-significant trend for symptom reduction (e.g. knee pain and physical function) in these RCTs. Two systematic reviews using aggregate data from these RCTs concluded that, although current evidence does not support vitamin D supplementation for reducing structural

disease progression, further research is needed to clarify the effects on patient-reported outcomes[18,19].

The null results of these RCTs could be due to a low prevalence of vitamin D deficiency in the study subjects or low statistical power secondary to small sample sizes. Another possible reason is that vitamin D may have an effect only in some OA phenotypes, such as those with BMLs (predominant bone abnormality)[20], effusion-synovitis (inflammatory)[21] or depressive symptoms (psychological distress)[13]. Post hoc analyses within these RCTs[15,21] were frequently underpowered, and hence unreliable to determine the effect of vitamin D treatment on subgroups of knee OA patients. A meta-analysis using IPD can increase the power of subgroup analysis by combining individual data from included trials[22] and therefore can quantify potential effect modifier of vitamin D treatment in subgroups.

Methods and analysis

We will conduct a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation in patients with symptomatic knee OA. The primary aim is to identify patient-level predictors of treatment response to vitamin D supplementation, including the status of vitamin D deficiency, MRI-detected bone marrow abnormalities and effusion-synovitis, and clinical signs of local inflammation. The protocol of this review is registered on the PROSPERO database (CRD42018107740).

Study eligibility

This systematic review will include studies that meet the following inclusion criteria:

Type of studies

RCTs that have been published in journals and reported the efficacy of vitamin D in participants with knee OA will be included. Cross-over design will also be eligible and only the first phase data will be included in the analysis. Both individually randomised trials and cluster randomised trials will be eligible. Both open-labelled and blinded studies will be eligible. There will be no language or geographical restrictions applied to study selection.

Participants

Men and women who have a diagnosis of knee OA, either according to the American College of Rheumatology criteria, or on the basis of detailed clinical and/or radiographic information, will be included. Studies with a subgroup of knee OA patients will also be included, provided that IPD can be collected separately for the OA subgroup.

Interventions

Only studies investigating oral supplementation of vitamin D will be included. Vitamin D treatments administered subcutaneously, intraperitoneally or intravenously will not be included. Both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) will be eligible, irrespective of preparations (tablet or capsule), dosage, regimen, and length of treatment.

Comparators

Oral vitamin D supplementation will be compared with control treatment including placebo or usual conservative care (pain medication and/or exercise therapy if they are used in both treatment and control groups).

Outcomes

The minimum criterion for inclusion is reporting pain or physical function as either primary or secondary outcomes. There will be no restrictions on the duration of follow-up. Data on other outcomes (e.g. patient's global assessment, quality of life, and adverse events) will be analysed when feasible but will not be required for study selection.

Baseline assessments

As a minimum, included studies should have measured knee pain, physical function, serum levels of vitamin D at baseline, and included basic patient characteristics such as age, gender, and BMI.

Literature search

A systematic literature search for articles published from 1 January 1990 until 31 December 2019 will be performed by a trained review author (XJ) in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE;

The search strategies used for each database are listed in *Appendix 1*. All retrieved articles will be exported to the reference manager *EndNote,* in which duplicates will be removed electronically and manually. The remaining records will be exported to an online systematic review management tool *Covidence* (Veritas Health Innovation, Melbourne, Australia) and the articles will be assessed for eligibility for inclusion. In addition to the electronic search, we will check the reference lists of included trials and previous systematic reviews to identify any trials that are not retrieved from the electronic search. Review authors and collaborating authors will be asked if they are aware of further relevant studies not yet included. We will also search the WHO International Clinical Trial Registration Platform Search Portal

(www.who.int/trialsearch) to identify any relevant trials that are completed but did not published the results.

Study selection

Two review authors (XJ, BA) will independently conduct study screening by assessing the article titles and abstracts. Full texts of the articles will be further assessed if the information from the abstract suggests that a study is eligible for inclusion. When information contained in the full text is not sufficient to make a judgement on its eligibility, we will make efforts to contact the corresponding authors to obtain further details. If a corresponding author is not contactable after two email attempts and one phone call, the study will be deemed ineligible. Any disagreement regarding the inclusion of a study will be discussed between the two review authors (XJ, BA). If no consensus can be reached, a third review author will be consulted (XW) to make a final decision.

Extraction of aggregate data

Study data extraction will be performed independently by two review authors (BA, XW). Discrepancies will be resolved by a third reviewer (XJ). We will extract the following study data from the included studies:

- General information: article title, bibliographic details, published language, and funding source.
- Participants: inclusion criteria, exclusion criteria, number of participants in total and in each study arm, study settings, and baseline participant characteristics (e.g. age, gender, BMI).
- Intervention: type of vitamin D preparation, dose, regimen, treatment duration, type of control, and co-interventions (if any).
- Outcomes: primary and secondary outcomes at the end of treatment and/or the end of follow-up. Number of withdrawals and loss to follow-up. Adverse events recorded.
- Data analysis: statistical models used for data analysis, confounding factors adjusted in the models, and methods used for addressing missing values.

Risk of bias assessment

The methodological quality of the included studies will be assessed using a modified version of the Cochrane's risk of bias tool[23]. The modified version includes all the seven domains of the original tool, but further separates performance bias assessment into 'blinding of participants' and 'blinding of study personnel', as well as pre-specifies other sources of bias as

'balance in baseline covariates', 'treatment compliance', and 'timely outcome assessment' (*Appendix 2*). Each domain will be scored as 'low risk', 'high risk' or 'unclear' according to the criteria described in the *Appendix 3*. The overall rating of risk of bias is based on the number of domains with a 'high-risk' score. The overall rating is intended to inform readers of the risk of bias across individual studies and will not be used to weight the studies in the meta-analysis. Two review authors (XJ, XW) will independently evaluate the quality of an individual study. Any disagreement will be settled by further discussion until a consensus is reached between the two review authors.

IPD collection and transfer

The primary or corresponding authors of included trials will be invited to collaborate on the project and contribute their raw data. When we cannot reach a corresponding author after sending two emails and making two telephone calls, we will contact the co-authors listed in the article. If none of the co-authors can be contacted, we will approach the institutes, in which the trial has been conducted. All data custodians will be asked to sign a data delivery agreement, which includes items regarding IPD delivery, obligations, ownership of data, terms and conditions of the use of the data, authorship, and publications. If needed, the project coordinator (XJ) will visit the institutes of the data deliverers to retrieve the data and to sign the data delivery agreement on behalf of the OA Trial Bank. De-identified datasets will be accepted in any electronic format (for example, SPSS, Stata, SAS, Excel) or in paper form, provided that variables and categories are adequately labelled within the dataset or within a separate codebook. The IPD files received by the coordinator will be kept in their original version and saved on a secured password-protected server at Erasmus MC Medical University in Rotterdam. The datasets will not be used for any other research apart from that described in the license agreement.

To ensure the quality of the data, the coordinator will independently check for data consistency by comparing the summary statistics derived from the IPD received against the summary results reported in the published articles. In the case of differences, the project coordinator will communicate with the data deliverer via email or teleconference to resolve the discrepancy.

Variables of interest

The following IPD variables will be obtained (where available):

Primary outcome variables

The primary outcomes for this meta-analysis will be pain and physical function at long-term follow-up (12 months or more).

- Knee pain will be evaluated using visual analogue scale (VAS) if available, otherwise the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[24] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[25] will be used. The pain data will be converted into a 0-100 common scale as recommended by the WOMAC manual[26].
- Physical function will be evaluated using a validated instrument specific to knee OA, such as the physical function subscales of the WOMAC or the KOOS subscales. The scores will be standardised into a 0-100 scale.

Secondary outcome variables

Secondary outcomes will include:

- Medium-term (more than 6 months but less than 12 months) pain and physical function;
- Short-term (less than 6 months) pain and physical function;
- Patient global assessment at the end of study follow-up, as recommended by the OMERACT-OARSI Initiative[27].
- Quality of life evaluated using a validated instrument, such as EQ-5D[28], osteoarthritis Knee and Hip Quality of Life (OAKHQOL)[29], or original instrument used in the included studies;
- Adverse events if reported, including all major and minor events such as hypocalcaemia, fractures, and depression.

Potential treatment effect moderators

If data are available, we will analyse potential treatment effect modification for the following variables measured at baseline:

- Radiographic stage of knee OA (mild/moderate or severe). Radiographic knee OA should be staged at baseline using either the Kellgren-Lawrence (KL)[30] or Osteoarthritis Research Society International (OARSI) joint space narrowing (JSN) grading system[31]. The results from the two grading systems have been shown to be highly correlated[32]. Mild to moderate disease will be defined as a KL score ≤ 3 or an OARSI JSN score ≤ 2, and severe disease will be a KL score of 4, or an OARSI score of 3.
- Vitamin D level (deficiency, insufficiency, or sufficiency). Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥50 nmol/L is considered as vitamin D sufficiency[33].

- Presence of BMLs (yes or no). BMLs at the patella-femoral and femoro-tibial joints should be measured by MRI using a validated scoring system, such as BLOKS (Boston Leeds Osteoarthritis Knee Score)[34], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[35], or KOSS (Knee Osteoarthritis Scoring System)[36].
- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination - tumor (swelling), dolor (pain), rubor (redness), calor (heat), and functio laesa (disturbance of function) - or by additional laboratory testing (e.g. serum c-reactive protein and erythrocyte sedimentation rate). Effusion-synovitis should be measured on either ultrasound or MRI.
- Presence of depressive symptoms or comorbid depression. Depressive symptoms are measured using a validated questionnaire, such as the Patient Health Questionnaire (PHQ-9)[37] and the Geriatric Depression Scale (GDS)[38].

Data synthesis and statistical methods

All statistical analysis will be conducted using R version 3.5.0 and RStudio (version 1.0.136, RStudio, Inc., Boston, MA), with R extension package 'metafor' for the conventional meta-analysis and two-stage IPD meta-analysis, and 'lme4' for the one-stage IPD meta-analysis.

Conventional meta-analysis

An aggregate data meta-analysis, using a random-effects model based on the 'DerSimonian and Laird' method[39], will be performed to estimate the treatment effect of vitamin D over control. The results will be compared with the IPD meta-analysis findings as sensitivity analyses.

Heterogeneity will be assessed by inspecting the forest plots and tested by χ^2 test. A result of $p<0.10$ will be defined as evidence of significant heterogeneity across studies. I^2 test will be used to estimate the extent of inconsistency across studies that is due to heterogeneity[40]. A result of over 30% and 50% represents moderate and substantial heterogeneity, respectively[41]. Sources of heterogeneity will be explored by excluding individual trials causing an I^2 score below 50%.

If 10 trials or more trials are available, we will use a Doi plot (normal quantile versus effect size plot) explore publication bias and 'small-study effects'[42]. Asymmetry in the Doi plot will be detected and quantified by the LFK index. A value beyond +/- 1 will be deemed consistent with asymmetry, thus having considerable small-study effects[42].

IPD meta-analysis

IPD from included trials will be recoded and formatted in a consistent way to permit re-analysis. A new variable will be created to indicate the trial in which the IPD are collected. The method used to handle missing data will depend on the mechanism causing the missingness. If no explanation is known for the reason of missing data, they will be assumed to be missing at random. We will use the R MICE package[43] for multiple imputation and the imputation model will include all available patient variables to help predict missing data for the variables of interest within each study dataset. The imputation procedure will use 20 imputed datasets. A sensitivity analyses will be performed restricting to participants without missing data (complete case analysis).

Both the treatment effect of vitamin D supplementation and the effect of potential moderators will be studied in the IPD meta-analyses. The treatment effect of vitamin D will be measured using the mean difference in knee pain and physical function between treatment and control based on the intention-to-treat principle. The interaction between the treatment and a potential moderator will be used to identify the effect of the moderator. Interaction effects with $p<0.05$ will be considered statistically significant and 95% confidence intervals of the effects will be provided. The IPD meta-analyses will be undertaken using both the one-stage and two-stage approaches. We will use the one-stage approach as the primary analysis to avoid assumptions of within-study normality and known within-study variance[44]. We will and compare the results to the two-stage approach to assess consistency in a sensitivity analysis.

One-stage modelling

The one-stage mixed-effects IPD meta-analysis approach will take into account both study level and subject-level covariates. Subject -level covariates will be centred to the mean of the covariate in each trial to avoid ecological bias. Three multilevel regression models will be built, the first to examine the summary treatment effect (difference between vitamin D and control), the second to evaluate each of the mentioned moderators on treatment effect, and the third to assess the true effect of one moderator independent of other moderators.

The first model will include outcome measure (e.g. pain score at follow-up) as a dependent variable, treatment (vitamin D or control), baseline subject-level covariate (e.g. pain score) and confounders (age, gender and BMI) as fixed-effect independent variables, adjusted for study identifier (random intercept). The partial regression coefficient of the treatment will be used to compare to the conventional meta-analysis.

The second model will further add the moderator of interest (e.g. radiographic stage of the disease) and interaction term between the treatment and study-centred values of the moderator

in the fixed-effect of the first model. The regression coefficient of the interaction term will be used to quantify the impact of the moderator on treatment effect.

If there are two or more moderators that have a statistically significant interaction with the treatment effect, these moderators will be incorporated in the third model. Multicollinearity between moderators will be tested before building the third model. A correlation coefficient r>0.80 will indicate that multiple collinearity exists between the two moderators, of which the one that has less measurement error will be included in the model.

Two-stage modelling

In the first stage, treatment effect and variance are derived from separate analysis in each study. An analysis of covariance (ANCOVA) model adjusted for baseline covariates (age, gender, BMI, as well as knee pain or function), will be used to obtain the treatment effect and variance within each study separately. The effect of a moderator and its variance within each study will be obtained by adding the interaction term between treatment effect and the moderator into the model. In the second stage, the treatment effect and its variances obtained from the first stage will be pooled across studies using a random-effects model[39]. The result of this model is a summary estimate of the treatment effect of vitamin D versus control. The effect of a moderator will be calculated by pooling the regression coefficient and variance of the interaction term between the treatment and the moderator using a similar model. If two or more interaction terms are statistically significant, these moderators will be incorporated in a further model to evaluate the independent effect of these moderators

Discussion

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial[7,18]. In a few existing RCTs in patients with symptomatic knee OA[27,14,16,17], small to modest improvement in knee pain and physical function were observed in participants receiving vitamin D supplementation, but the treatment response varies considerably and the effects were not statistically significant when compared to placebo. The broad variation in treatment response could be a result of the fact that knee OA is a highly heterogenous disease with multiple aetiologies[45]. Vitamin D may therefore be more effective in a subset of patients with specific characteristics than others. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short- and long-term follow-up.

An IPD meta-analysis is the grandmother of 'big data'[46] and an integrated part of precision medicine[47]. It is a cost-effective approach to identify potential moderators of treatment response at a patient level, which is not possible with subgroup analyses in a single trial or conventional meta-analysis with aggregate data[48]. Subgroup analyses within individual trials are often underpowered to generate reliable findings. In contrast, IPD meta-analysis techniques increase the statistical power of the study by combining individual observation data from multiple trials with the same treatment[22]. This offers greater precision in analysing moderators of treatment response and offers the potential to analyse a greater number of moderators. In conventional meta-analysis, meta-regression analysis may be used to examine differences in the types of patients enrolled in individual trials, but is potentially problematic. Meta-regression analysis may make incorrect inferences about individual characteristics based upon aggregate baseline statistics reported in trial publications[49]. This is also known as ecological fallacy[50], where the relationship between the effect estimate and average patient characteristics across trials may not be the same as the relationship within individual trials.

Identifying different phenotypes of knee OA is currently a popular subject of research in the field. Different phenotyping strategies have been proposed based on risk factors from epidemiological studies[51], anatomical abnormalities on modern imaging[52], or molecular abnormalities related to pathological mechanisms[53]. While there is currently no standardised classification system for knee OA phenotypes[5], we believe that disease phenotypes are most meaningful when they reflect differential treatment effects. IPD meta-analysis provides an opportunity to assess the effect of treatments on subtypes or phenotypes of patients with knee OA according to predefined set of characteristics. The current proposed IPD meta-analysis attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

Strengths and limitations

Several challenges may present when conducting an IPD meta-analysis. First, although IPD meta-analyses usually offer sufficient statistical power to examine moderators of treatment response, not all RCTs measure potential moderators of interest or measure them in the same way. This may limit the analysis to only exploring moderators that have been collected across studies. The current protocol attempts to minimise this risk by including moderators that are commonly reported in OA research. In addition, there are expected barriers to accessing data, such as the authors of included trials not being able to be contacted, or the authors losing access to raw data or not choosing to collaborate, may introduce selection bias into the IPD meta-

analysis. However, this could be examined in sensitivity analyses by comparing the results to the conventional meta-analysis or be addressed using frameworks that combine IPD and aggregate data in a meta-analysis[54].

The benefits of using IPD meta-analysis techniques greatly outweigh the challenges of using this intensive method. Previous RCTs and systematic reviews have not had sufficient power to thoroughly examine the differential treatment response of vitamin D supplementation in different subsets of patients with knee OA.

The results of this project have a high potential to provide important evidence to guide subgroup-specific treatment decisions in clinical practice to improve therapeutic effectiveness.

Status of project

Currently, literature search in the electronic databases has been commenced.

Abbreviations

OA: osteoarthritis; IPD: individual patient data; RCT: randomised controlled trial; BMI: body mass index; MRI: magnetic resonance imaging; BMLs: bone marrow lesions; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International.

Additional Information

Acknowledgement

We acknowledge the University of Sydney China Study Centre for providing short-term travel support to establish international collaboration for this project.

Ethics approval and consent to participate

Research ethical or governance approval is exempt for this study as no new data are being collected.

Availability of data and material

Data are available upon reasonable request.

Authors contributions

All authors were involved in the study design and all will contribute to the interpretation of the results. CD, BA and XJ concepted this study. WZ and MP provided methodological support for statistical analysis. XJ and BA will contact the potential data delivers and will coordinate the project. CD, FC, TM, NA, RNS and SRS will deliver relevant data from their completed trials. SBZ and MM will facilitate legal agreement for data transfer and provide database management at the OA Trial Bank. XJ, BA and XW will perform the study selection, risk of bias assessment, data collection and analysis. All authors contributed to writing of this manuscript and approved the final submission.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and public involvement

We do not directly include patient and public involvement in this study, but the design of included randomised controlled trials may involve patients.

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Appendix 1. Search strategy

Cochrane CENTRAL

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab,kw

#3. (degenerative near/2 arthritis):ti,ab,kw

#4. coxarthrosis:ti,ab,kw

#5. (#1 OR #2 OR #3 OR #4)

#6. MeSH desclriptor vitamin D explode all trees

#7. (vitamin D):ti,ab,kw

#8. (vitamin D2):ti,ab,kw

#9. (vitamin D3):ti,ab,kw

#10. (1-alpha hydroxyvitamin D3):ti,ab,kw

#11. (1-alpha-hydroxy-vitamin D3):ti,ab,kw

#12. (1-alpha hydroxycalciferol):ti,ab,kw

#13. (1-alpha-hydroxy-calciferol):ti,ab,kw

#14. (1,25 dihydroxyvitamin D3):ti,ab,kw

#15. (1,25-dihydroxy-vitamin D3):ti,ab,kw

#16. (1,25 dihydroxycholecalciferol):ti,ab,kw

#17. (1,25-dihydroxycholecalciferol):ti,ab,kw

#18. (25-hydroxycholecalciferol):ti,ab,kw

#19. (25 hydroxycholecalciferol):ti,ab,kw

#20. (25 hydroxyvitamin D):ti,ab,kw

#21. (25-hydroxy-vitamin D):ti,ab,kw

#22. (alfacalcidol):ti,ab,kw

#23. (calcidiol):ti,ab,kw

#24. (calcitriol):ti,ab,kw

#25. (calcifediol):ti,ab,kw

#26. (calciferol):ti,ab,kw

#27. (ergocalciferol):ti,ab,kw

#28. (cholecalciferol):ti,ab,kw

#29. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)

#30. #5 AND #29

MEDLINE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials.sh.
33. random allocation.sh.
34. double blind method.sh.

35. single-blind method.sh.
36. clinical trial.pt.
37. clinical trials.sh.
38. clinical trial.tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
40. placebos.sh.
41. placebo$.tw.
42. random$.tw.
43. Research Design/
44. comparative study.sh.
45. evaluation studies.sh.
46. follow-up studies.sh.
47. prospective studies.sh.
48. control$.tw.
49. prospectiv$.tw.
50. volunteer$.tw.
51. or/30-50
52. (animal not human).mp.
53. 46 not 47
54. 5 and 29 and 53

EMBASE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. random$.tw.
31. factorial$.tw.
32. crossover$.tw.
33. cross over$.tw.
34. cross-over$.tw.

35. placebo$.tw.
36. (doubl$ adj blind$).tw.
37. (singl$ adj blind$).tw.
38. assign$.tw.
39. allocat$.tw.
40. volunteer$.tw.
41. Crossover Procedure/
42. double-blind procedure.tw.
43. Randomized Controlled Trial/
44. Single Blind Procedure/
45. or/30-44
46. (animal/ or nonhuman/) not human/
47. 45 not 46
48. 5 and 29 and 47

Appendix 2. Modified Cochrane's risk of bias tool.

Source of bias[#]	Low risk	High risk	Unclear	Comments
1. Random sequence generation	☐	☐	☐	
2. Allocation concealment	☐	☐	☐	
3. Blinding of participants	☐	☐	☐	
4. Blinding of key study personnel	☐	☐	☐	
5. Blinding of outcome assessment	☐	☐	☐	
6. Incomplete outcome data	☐	☐	☐	
7. Selective outcome reporting	☐	☐	☐	
8. Imbalance in baseline covariates	☐	☐	☐	
9. Treatment compliance	☐	☐	☐	
10. Timing of outcome assessment	☐	☐	☐	
Overall risk of bias	**Low**	**Moderate**	**High**	
	☐	☐	☐	

[#]See *Appendix 2* for criteria for different levels of risk.

Appendix 3. Criteria for risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Sequence generation process involves judgement or some method of non-random categorisation of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of "High risk":

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2
Authors					
Contact	3a	Provide name, institutional affiliation, and 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 15
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	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 5
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	☒	☐	Page 5, Appendix 1.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8-10
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 8-9
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 7, Appendix 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-12
	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 (e.g., I^2, Kendall's tau)	☒	☐	Page 10-12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	N/A

BMJ Open

The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA) - An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035302.R2
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The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA)

An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

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Systematic Review; Meta-analysis; Individual Patient Data; Osteoarthritis; Vitamin D; Knee.

Abstract

Introduction

Observational data suggest vitamin D deficiency is associated with the onset and progression of knee OA. However, randomized controlled trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Further research is needed to clarify the effects of vitamin D on patient-reported outcomes and determine whether there are patient subgroups who may benefit from the supplementation. The aim of this IPD meta-analysis is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function.

Methods and analysis

A systematic literature search will be conducted for RCTs of vitamin D supplementation on knee OA. Authors of original RCTs will be contacted to obtain the IPD. The primary outcomes will include long-term ($\geqslant$12 months) pain and physical function. Secondary outcomes will include medium-term ($\geqslant$6 months and <12 months) and short-term (<6 months) pain and physical function, as well as patient global assessment, quality of life and adverse events. Potential treatment effect modifiers to be examined in the subgroup analyses include age, gender, body mass index (BMI), baseline knee pain severity and physical function, baseline vitamin D level, radiographic stage, presence of bone marrow lesions on magnetic resonance images (MRI), presence of clinical signs of local inflammation, and concomitant depressive symptoms. Both one-step and two-step modelling methods will be used to determine the possible modifiable effect of each subgroup of interest.

Ethics and dissemination

Separate ethics committee approval because this study involves analysis of de-identified data that have already been collected in individual RCTs. This study will be the first IPD meta-analysis to clarify the effect of vitamin D supplementation on clinical symptoms in different subgroups of patients with knee OA. The findings will be disseminated through peer-review publications and conference presentations.

Systematic review registration

This systematic review is registered on PROSPERO (CRD42018107740).

Article Summary

This article is a protocol for a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation on joint pain and physical function in patients with symptomatic knee OA.

Strengths and limitations of this study

- This study protocol is endorsed by the OA Trial Bank, an international collaboration that initiates meta-analyses on predefined subgroups of OA patients.
- This study is the first IPD meta-analysis to identify OA patient subgroups that may benefit from vitamin D supplementation.
- IPD meta-analysis offer greater statistical power and precision than subgroup analysis in a single trial and conventional meta-analysis using aggregate data.
- Analysis may be limited to the variables that have been collected across included RCTs.

Introduction

OA is the most common joint disorder worldwide. OA is ranked as the 13th highest contributor of 310 diseases to global disability in 2015[1]. In Australia, OA affects over 2.1 million people (9% of the population), costing the healthcare system over $2.1 billion in 2015[2]. This cost is forecasted to increase by 41% in 2030[3].

The majority (83%) of the disease burden of OA is attributable to knee OA[4], which is characterized by pain, gradual loss of articular cartilage, and structural changes such as subchondral remodelling and effusion-synovitis[5]. Currently, there are no effective disease-modifying treatments to reverse the progression of knee OA once the disease is established. A majority of patients with knee OA eventually progress to advanced stage and undergo total knee replacement[6]. There is clearly an urgent need for innovative and cost-effective approaches to slow the progression of knee OA.

Emerging observational data suggest that vitamin D insufficiency is associated with the onset and progression of knee OA[7]. The association between low serum vitamin D levels and knee OA symptoms may be explained by a direct effect of vitamin D on chondrocytes in osteoarthritic cartilage[8], as well as indirect effects on subchondral bone, synovium, and periarticular muscle[9]. For example, vitamin D deficiency could impair the ability of bone to respond optimally to pathological bone marrow lesions (BMLs) and altered bone mineral density, therefore predisposing the knees to disease progression[10]. Vitamin D also may reduce synovitis in affected knees by regulating cytokine levels in the joint, leading to a reduction in the amount of effusion-synovitis in MRI[11]. In addition, depressive symptoms is interrelated to joint pain in OA[12], and maintaining sufficient serum vitamin D may improve depression symptoms in patients with knee OA[13].

However, evidence from RCTs have been conflicting[14–17]. A pilot RCT in India found a small but statistically significant clinical benefit for 12-month vitamin D treatment on pain and function in patients with knee OA, compared with placebo[3916]. In contrast, a subsequent RCT from the US showed that vitamin D supplementation did not reduce knee pain or cartilage volume loss over 24 months[15]. Subsequently, data from RCTs in Australia[17] and UK[14] did not find significant clinical benefits of vitamin D supplementation for knee OA. However, there was a non-significant trend for symptom reduction (e.g. knee pain and physical function) in these RCTs. Two systematic reviews using aggregate data from these RCTs concluded that, although current evidence does not support vitamin D supplementation for reducing structural

disease progression, further research is needed to clarify the effects on patient-reported outcomes[18,19]. There are no systematic reviews of previous systematic reviews on this topic.

The null results of these RCTs could be due to a low prevalence of vitamin D deficiency in the study subjects or low statistical power secondary to small sample sizes. Another possible reason is that vitamin D may have an effect only in some OA phenotypes, such as those with BMLs (predominant bone abnormality)[20], effusion-synovitis (inflammatory)[21] or depressive symptoms (psychological distress)[13]. Post hoc analyses within these RCTs[15,21] were frequently underpowered, and hence unreliable to determine the effect of vitamin D treatment on subgroups of knee OA patients. A meta-analysis using IPD can increase the power of subgroup analysis by combining individual data from included trials[22] and therefore can quantify potential effect modifier of vitamin D treatment in subgroups.

Methods and analysis

We will conduct a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation in patients with symptomatic knee OA. The primary aim is to identify patient-level predictors of treatment response to vitamin D supplementation, including the status of vitamin D deficiency, MRI-detected bone marrow abnormalities and effusion-synovitis, and clinical signs of local inflammation. The protocol of this review is registered on the PROSPERO database (CRD42018107740).

Study eligibility

This systematic review will include studies that meet the following inclusion criteria:

Type of studies

RCTs that have been published in journals and reported the efficacy of vitamin D in participants with knee OA will be included. Cross-over design will also be eligible and only the first phase data will be included in the analysis. Both individually randomised trials and cluster randomised trials will be eligible. Both open-labelled and blinded studies will be eligible. There will be no language or geographical restrictions applied to study selection.

Participants

Men and women who have a diagnosis of knee OA, either according to the American College of Rheumatology criteria, or on the basis of detailed clinical and/or radiographic information, will be included. Studies with a subgroup of knee OA patients will also be included, provided that IPD can be collected separately for the OA subgroup. Although most patients with knee OA defined by the American College of Rheumatology are usually over 50 years of age, the

disease can occur as early as 20 years old, therefore studies with adults at 18 years of age and older will be included.

Interventions

Only studies investigating oral supplementation of vitamin D will be included. Vitamin D treatments administered subcutaneously, intraperitoneally or intravenously will not be included. Both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) will be eligible, irrespective of preparations (tablet or capsule), dosage, regimen, and length of treatment.

Comparators

Oral vitamin D supplementation will be compared with control treatment including placebo or usual conservative care (pain medication and/or exercise therapy if they are used in both treatment and control groups).

Outcomes

The minimum criterion for inclusion is reporting pain or physical function as either primary or secondary outcomes. There will be no restrictions on the duration of follow-up. Data on other outcomes (e.g. patient's global assessment, quality of life, and adverse events) will be analysed when feasible but will not be required for study selection.

Baseline assessments

As a minimum, included studies should have measured knee pain, physical function, serum levels of vitamin D at baseline, and included basic patient characteristics such as age, gender, and BMI.

Literature search

A systematic literature search for articles published from 1 January 1990 until 31 December 2019 will be performed by a trained review author (XJ) in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE;

A previous systematic review[7] has showed that no major RCTs were conducted for vitamin D and osteoarthritis by the year 1990, therefore we choose 1 January 1990 as the start date of the literature search. The search strategies used for each database are listed in *Appendix 1*. All retrieved articles will be exported to the reference manager *EndNote,* in which duplicates will be removed electronically and manually. The remaining records will be exported to an online systematic review management tool *Covidence* (Veritas Health Innovation, Melbourne, Australia) and the articles will be assessed for eligibility for inclusion. In addition to the

electronic search, we will check the reference lists of included trials and previous systematic reviews to identify any trials that are not retrieved from the electronic search. Review authors and collaborating authors will be asked if they are aware of further relevant studies not yet included. We will also search the WHO International Clinical Trial Registration Platform Search Portal (www.who.int/trialsearch) to identify any relevant trials that are completed but did not published the results.

Study selection

Two review authors (XJ, BA) will independently conduct study screening by assessing the article titles and abstracts. Full texts of the articles will be further assessed if the information from the abstract suggests that a study is eligible for inclusion. When information contained in the full text is not sufficient to make a judgement on its eligibility, we will make efforts to contact the corresponding authors to obtain further details. If a corresponding author is not contactable after two email attempts and one phone call, the study will be deemed ineligible. Any disagreement regarding the inclusion of a study will be discussed between the two review authors (XJ, BA). If no consensus can be reached, a third review author will be consulted (XW) to make a final decision.

Extraction of aggregate data

Study data extraction will be performed independently by two review authors (BA, XW). Discrepancies will be resolved by a third reviewer (XJ). We will extract the following study data from the included studies:

- General information: article title, bibliographic details, published language, and funding source.
- Participants: inclusion criteria, exclusion criteria, number of participants in total and in each study arm, study settings, and baseline participant characteristics (e.g. age, gender, BMI).
- Intervention: type of vitamin D preparation, dose, regimen, treatment duration, type of control, and co-interventions (if any).
- Outcomes: primary and secondary outcomes at the end of treatment and/or the end of follow-up. Number of withdrawals and loss to follow-up. Adverse events recorded.
- Data analysis: statistical models used for data analysis, confounding factors adjusted in the models, and methods used for addressing missing values.

Risk of bias assessment

The methodological quality of the included studies will be assessed using a modified version of the Cochrane's risk of bias tool[23]. The modified version includes all the seven domains of the original tool, but further separates performance bias assessment into 'blinding of participants' and 'blinding of study personnel', as well as pre-specifies other sources of bias as 'balance in baseline covariates', 'treatment compliance', and 'timely outcome assessment' (*Appendix 2*). Each domain will be scored as 'low risk', 'high risk' or 'unclear' according to the criteria described in the *Appendix 3*. The overall rating of risk of bias is based on the number of domains with a 'high-risk' score. The overall rating is intended to inform readers of the risk of bias across individual studies and will not be used to weight the studies in the meta-analysis. Two review authors (XJ, XW) will independently evaluate the quality of an individual study. Any disagreement will be settled by further discussion until a consensus is reached between the two review authors.

IPD collection and transfer

The primary or corresponding authors of included trials will be invited to collaborate on the project and contribute their raw data. When we cannot reach a corresponding author after sending two emails and making two telephone calls, we will contact the co-authors listed in the article. If none of the co-authors can be contacted, we will approach the institutes, in which the trial has been conducted. All data custodians will be asked to sign a data delivery agreement, which includes items regarding IPD delivery, obligations, ownership of data, terms and conditions of the use of the data, authorship, and publications. If needed, the project coordinator (XJ) will visit the institutes of the data deliverers to retrieve the data and to sign the data delivery agreement on behalf of the OA Trial Bank (the detailed procedures of data delivery and an example of the data delivery agreement can be found on the OA Trial Bank website https://www.oatrialbank.com/procedures/). De-identified datasets will be accepted in any electronic format (for example, SPSS, Stata, SAS, Excel) or in paper form, provided that variables and categories are adequately labelled within the dataset or within a separate codebook. The IPD files received by the coordinator will be kept in their original version and saved on a secured password-protected server at Erasmus MC Medical University in Rotterdam. The datasets will not be used for any other research apart from that described in the license agreement.

To ensure the quality of the data, the coordinator will independently check for data consistency by comparing the summary statistics derived from the IPD received against the summary

results reported in the published articles. In the case of differences, the project coordinator will communicate with the data deliverer via email or teleconference to resolve the discrepancy.

Variables of interest

The following IPD variables will be obtained (where available):

Primary outcome variables

The primary outcomes for this meta-analysis will be pain and physical function at long-term follow-up (12 months or more). This definition of 'long-term effect' for knee OA treatment was used in previous systematic reviews of knee OA research[24,25].

- Knee pain will be evaluated using visual analogue scale (VAS) if available, otherwise the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[26] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[27] will be used. The pain data will be converted into a 0-100 common scale as recommended by the WOMAC manual[28].
- Physical function will be evaluated using a validated instrument specific to knee OA, such as the physical function subscales of the WOMAC or the KOOS subscales. The scores will be standardised into a 0-100 scale.

Secondary outcome variables

Secondary outcomes will include:

- Medium-term (more than 6 months but less than 12 months) pain and physical function;
- Short-term (less than 6 months) pain and physical function;
- Patient global assessment at the end of study follow-up, as recommended by the OMERACT-OARSI Initiative[29].
- Quality of life evaluated using a validated instrument, such as EQ-5D[30], osteoarthritis Knee and Hip Quality of Life (OAKHQOL)[31], or original instrument used in the included studies;
- Adverse events if reported, including all major and minor events such as hypocalcaemia, fractures, and depression.

Potential treatment effect moderators

If data are available, we will analyse potential treatment effect modification for the following variables measured at baseline:

- Radiographic stage of knee OA (mild/moderate or severe). Radiographic knee OA should be staged at baseline using either the Kellgren-Lawrence (KL)[32] or Osteoarthritis Research

Society International (OARSI) joint space narrowing (JSN) grading system[33]. The results from the two grading systems have been shown to be highly correlated[34]. Mild to moderate disease will be defined as a KL score ≤ 3 or an OARSI JSN score ≤ 2, and severe disease will be a KL score of 4, or an OARSI score of 3.

- Vitamin D level (deficiency, insufficiency, or sufficiency). Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥50 nmol/L is considered as vitamin D sufficiency[35].
- Presence of BMLs (yes or no). BMLs at the patella-femoral and femoro-tibial joints should be measured by MRI using a validated scoring system, such as BLOKS (Boston Leeds Osteoarthritis Knee Score)[36], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[37], or KOSS (Knee Osteoarthritis Scoring System)[38].
- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination - tumor (swelling), dolor (pain), rubor (redness), calor (heat), and functio laesa (disturbance of function) - or by additional laboratory testing (e.g. serum c-reactive protein and erythrocyte sedimentation rate). Effusion-synovitis should be measured on either ultrasound or MRI.
- Presence of depressive symptoms or comorbid depression. Depressive symptoms are measured using a validated questionnaire, such as the Patient Health Questionnaire (PHQ-9)[39] and the Geriatric Depression Scale (GDS)[40].

Data synthesis and statistical methods

All statistical analysis will be conducted using R version 3.5.0 and RStudio (version 1.0.136, RStudio, Inc., Boston, MA), with R extension package 'metafor' for the conventional meta-analysis and two-stage IPD meta-analysis, and 'lme4' for the one-stage IPD meta-analysis.

Conventional meta-analysis

An aggregate data meta-analysis, using a random-effects model based on the 'DerSimonian and Laird' method[41], will be performed to estimate the treatment effect of vitamin D over control. If an included study is a cluster RCT, an approximately correct analysis will be performed to account for the effect of clustering[42]. The results will be compared with the IPD meta-analysis findings as sensitivity analyses.

Heterogeneity will be assessed by inspecting the forest plots and tested by χ^2 test. A result of $p<0.10$ will be defined as evidence of significant heterogeneity across studies. I^2 test will be

used to estimate the extent of inconsistency across studies that is due to heterogeneity[43]. A result of over 30% and 50% represents moderate and substantial heterogeneity, respectively[42]. Sources of heterogeneity will be explored by excluding individual trials causing an I^2 score below 50%.

If 10 trials or more trials are available, we will use a Doi plot (normal quantile versus effect size plot) explore publication bias and 'small-study effects'[44]. Asymmetry in the Doi plot will be detected and quantified by the LFK index. A value beyond +/- 1 will be deemed consistent with asymmetry, thus having considerable small-study effects[44].

IPD meta-analysis

IPD from included trials will be recoded and formatted in a consistent way to permit re-analysis. A new variable will be created to indicate the trial in which the IPD are collected. The method used to handle missing data will depend on the mechanism causing the missingness. If no explanation is known for the reason of missing data, they will be assumed to be missing at random. We will use the R MICE package[45] for multiple imputation and the imputation model will include all available patient variables to help predict missing data for the variables of interest within each study dataset. The imputation procedure will use 20 imputed datasets. A sensitivity analyses will be performed restricting to participants without missing data (complete case analysis).

Both the treatment effect of vitamin D supplementation and the effect of potential moderators will be studied in the IPD meta-analyses. The treatment effect of vitamin D will be measured using the mean difference in knee pain and physical function between treatment and control based on the intention-to-treat principle. The interaction between the treatment and a potential moderator will be used to identify the effect of the moderator. Interaction effects with $p<0.05$ will be considered statistically significant and 95% confidence intervals of the effects will be provided. The IPD meta-analyses will be undertaken using both the one-stage and two-stage approaches. We will use the one-stage approach as the primary analysis to avoid assumptions of within-study normality and known within-study variance[46]. We will and compare the results to the two-stage approach to assess consistency in a sensitivity analysis.

One-stage modelling

The one-stage mixed-effects IPD meta-analysis approach will take into account both study level and subject-level covariates. Subject -level covariates will be centred to the mean of the covariate in each trial to avoid ecological bias. Three multilevel regression models will be built, the first to examine the summary treatment effect (difference between vitamin D and control),

the second to evaluate each of the mentioned moderators on treatment effect, and the third to assess the true effect of one moderator independent of other moderators.

The first model will include outcome measure (e.g. pain score at follow-up) as a dependent variable, treatment (vitamin D or control), baseline subject-level covariate (e.g. pain score) and confounders (age, gender and BMI) as fixed-effect independent variables, adjusted for study identifier (random intercept). The partial regression coefficient of the treatment will be used to compare to the conventional meta-analysis.

The second model will further add the moderator of interest (e.g. radiographic stage of the disease) and interaction term between the treatment and study-centred values of the moderator in the fixed-effect of the first model. The regression coefficient of the interaction term will be used to quantify the impact of the moderator on treatment effect.

If there are two or more moderators that have a statistically significant interaction with the treatment effect, these moderators will be incorporated in the third model. Multicollinearity between moderators will be tested before building the third model. A correlation coefficient $r>0.80$ will indicate that multiple collinearity exists between the two moderators, of which the one that has less measurement error will be included in the model.

Two-stage modelling

In the first stage, treatment effect and variance are derived from separate analysis in each study. An analysis of covariance (ANCOVA) model adjusted for baseline covariates (age, gender, BMI, as well as knee pain or function), will be used to obtain the treatment effect and variance within each study separately. The effect of a moderator and its variance within each study will be obtained by adding the interaction term between treatment effect and the moderator into the model. In the second stage, the treatment effect and its variances obtained from the first stage will be pooled across studies using a random-effects model[41]. The result of this model is a summary estimate of the treatment effect of vitamin D versus control. The effect of a moderator will be calculated by pooling the regression coefficient and variance of the interaction term between the treatment and the moderator using a similar model. If two or more interaction terms are statistically significant, these moderators will be incorporated in a further model to evaluate the independent effect of these moderators.

Discussion

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial[7,18]. In a few existing RCTs

in patients with symptomatic knee OA[27,14,16,17], small to modest improvement in knee pain and physical function were observed in participants receiving vitamin D supplementation, but the treatment response varies considerably and the effects were not statistically significant when compared to placebo. The broad variation in treatment response could be a result of the fact that knee OA is a highly heterogenous disease with multiple aetiologies[47]. Vitamin D may therefore be more effective in a subset of patients with specific characteristics than others. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short- and long-term follow-up.

Meta-analysis is considered by some the grandmother of 'big data'[48] and an integrated part of precision medicine[49]. It is a cost-effective approach to identify potential moderators of treatment response at a patient level, which is not possible with subgroup analyses in a single trial or conventional meta-analysis with aggregate data[50]. Subgroup analyses within individual trials are often underpowered to generate reliable findings. In contrast, IPD meta-analysis techniques increase the statistical power of the study by combining individual observation data from multiple trials with the same treatment[22]. This offers greater precision in analysing moderators of treatment response and offers the potential to analyse a greater number of moderators. In conventional meta-analysis, meta-regression analysis may be used to examine differences in the types of patients enrolled in individual trials, but is potentially problematic. Meta-regression analysis may make incorrect inferences about individual characteristics based upon aggregate baseline statistics reported in trial publications[51]. This is also known as ecological fallacy[52], where the relationship between the effect estimate and average patient characteristics across trials may not be the same as the relationship within individual trials.

Identifying different phenotypes of knee OA is currently a popular subject of research in the field. Different phenotyping strategies have been proposed based on risk factors from epidemiological studies[53], anatomical abnormalities on modern imaging[54], or molecular abnormalities related to pathological mechanisms[55]. While there is currently no standardised classification system for knee OA phenotypes[5], we believe that disease phenotypes are most meaningful when they reflect differential treatment effects. IPD meta-analysis provides an opportunity to assess the effect of treatments on subtypes or phenotypes of patients with knee OA according to predefined set of characteristics. The current proposed IPD meta-analysis

attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

Strengths and limitations

Several challenges may present when conducting an IPD meta-analysis. First, although IPD meta-analyses usually offer sufficient statistical power to examine moderators of treatment response, not all RCTs measure potential moderators of interest or measure them in the same way. This may limit the analysis to only exploring moderators that have been collected across studies. The current protocol attempts to minimise this risk by including moderators that are commonly reported in OA research. In addition, there are expected barriers to accessing data, such as the authors of included trials not being able to be contacted, or the authors losing access to raw data or not choosing to collaborate, may introduce selection bias into the IPD meta-analysis. However, this could be examined in sensitivity analyses by comparing the results to the conventional meta-analysis or be addressed using frameworks that combine IPD and aggregate data in a meta-analysis[56].

The benefits of using IPD meta-analysis techniques greatly outweigh the challenges of using this intensive method. Previous RCTs and systematic reviews have not had sufficient power to thoroughly examine the differential treatment response of vitamin D supplementation in different subsets of patients with knee OA. The results of this project have a high potential to provide important evidence to guide subgroup-specific treatment decisions in clinical practice to improve therapeutic effectiveness.

Status of project

Currently, literature search in the electronic databases has been commenced.

Abbreviations

OA: osteoarthritis; IPD: individual patient data; RCT: randomised controlled trial; BMI: body mass index; MRI: magnetic resonance imaging; BMLs: bone marrow lesions; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International.

Additional Information

Acknowledgement

We acknowledge the University of Sydney China Study Centre for providing short-term travel support to establish international collaboration for this project.

Ethics approval and consent to participate

Research ethical or governance approval is exempt for this study as no new data are being collected.

Availability of data and material

Erasmus MC intends to create a central databank including data from several randomised clinical trials evaluating one or more interventions in patients with osteoarthritis of the knee or hip (the OA Trial Bank) in order to enable researchers to perform meta-analyses on individual patient data to define sub-groups that are specifically responsive to certain treatments. Data request for future research using data deposited in the OA Trial Bank can be directed to https://www.oatrialbank.com/contact/

Authors contributions

All authors were involved in the study design and all will contribute to the interpretation of the results. CD, BA and XJ concepted this study. WZ and MP provided methodological support for statistical analysis. XJ and BA will contact the potential data delivers and will coordinate the project. CD, FC, TM, NA, RNS and SRS will deliver relevant data from their completed trials. SBZ and MM will facilitate legal agreement for data transfer and provide database management at the OA Trial Bank. XJ, BA and XW will perform the study selection, risk of bias assessment, data collection and analysis. All authors contributed to writing of this manuscript and approved the final submission.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and public involvement

We do not directly include patient and public involvement in this study, but the design of included randomised controlled trials may involve patients.

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Appendix 1. Search strategy

Cochrane CENTRAL

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab,kw

#3. (degenerative near/2 arthritis):ti,ab,kw

#4. coxarthrosis:ti,ab,kw

#5. (#1 OR #2 OR #3 OR #4)

#6. MeSH desclriptor vitamin D explode all trees

#7. (vitamin D):ti,ab,kw

#8. (vitamin D2):ti,ab,kw

#9. (vitamin D3):ti,ab,kw

#10. (1-alpha hydroxyvitamin D3):ti,ab,kw

#11. (1-alpha-hydroxy-vitamin D3):ti,ab,kw

#12. (1-alpha hydroxycalciferol):ti,ab,kw

#13. (1-alpha-hydroxy-calciferol):ti,ab,kw

#14. (1,25 dihydroxyvitamin D3):ti,ab,kw

#15. (1,25-dihydroxy-vitamin D3):ti,ab,kw

#16. (1,25 dihydroxycholecalciferol):ti,ab,kw

#17. (1,25-dihydroxycholecalciferol):ti,ab,kw

#18. (25-hydroxycholecalciferol):ti,ab,kw

#19. (25 hydroxycholecalciferol):ti,ab,kw

#20. (25 hydroxyvitamin D):ti,ab,kw

#21. (25-hydroxy-vitamin D):ti,ab,kw

#22. (alfacalcidol):ti,ab,kw

#23. (calcidiol):ti,ab,kw

#24. (calcitriol):ti,ab,kw

#25. (calcifediol):ti,ab,kw

#26. (calciferol):ti,ab,kw

#27. (ergocalciferol):ti,ab,kw

#28. (cholecalciferol):ti,ab,kw

#29. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)

#30. #5 AND #29

MEDLINE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials.sh.
33. random allocation.sh.
34. double blind method.sh.

35. single-blind method.sh.
36. clinical trial.pt.
37. clinical trials.sh.
38. clinical trial.tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
40. placebos.sh.
41. placebo$.tw.
42. random$.tw.
43. Research Design/
44. comparative study.sh.
45. evaluation studies.sh.
46. follow-up studies.sh.
47. prospective studies.sh.
48. control$.tw.
49. prospectiv$.tw.
50. volunteer$.tw.
51. or/30-50
52. (animal not human).mp.
53. 46 not 47
54. 5 and 29 and 53

EMBASE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. random$.tw.
31. factorial$.tw.
32. crossover$.tw.
33. cross over$.tw.
34. cross-over$.tw.

35. placebo$.tw.
36. (doubl$ adj blind$).tw.
37. (singl$ adj blind$).tw.
38. assign$.tw.
39. allocat$.tw.
40. volunteer$.tw.
41. Crossover Procedure/
42. double-blind procedure.tw.
43. Randomized Controlled Trial/
44. Single Blind Procedure/
45. or/30-44
46. (animal/ or nonhuman/) not human/
47. 45 not 46
48. 5 and 29 and 47

Appendix 2. Modified Cochrane's risk of bias tool.

Source of bias[#]	Low risk	High risk	Unclear	Comments
1. Random sequence generation	☐	☐	☐	
2. Allocation concealment	☐	☐	☐	
3. Blinding of participants	☐	☐	☐	
4. Blinding of key study personnel	☐	☐	☐	
5. Blinding of outcome assessment	☐	☐	☐	
6. Incomplete outcome data	☐	☐	☐	
7. Selective outcome reporting	☐	☐	☐	
8. Imbalance in baseline covariates	☐	☐	☐	
9. Treatment compliance	☐	☐	☐	
10. Timing of outcome assessment	☐	☐	☐	
Overall risk of bias	**Low**	**Moderate**	**High**	
	☐	☐	☐	

[#]See *Appendix 2* for criteria for different levels of risk.

Appendix 3. Criteria for risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Sequence generation process involves judgement or some method of non-random categorisation of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of "High risk":

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2
Authors					
Contact	3a	Provide name, institutional affiliation, and 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 15
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	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 5
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	☒	☐	Page 5, Appendix 1.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8-10
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 8-9
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 7, Appendix 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-12
	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 (e.g., I^2, Kendall's tau)	☒	☐	Page 10-12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	N/A

BMJ Open

The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA) - An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

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The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA)

An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

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Keywords

Systematic Review; Meta-analysis; Individual Patient Data; Osteoarthritis; Vitamin D; Knee.

Abstract

Introduction

Observational data suggest vitamin D deficiency is associated with the onset and progression of knee OA. However, randomized controlled trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Further research is needed to clarify the effects of vitamin D on patient-reported outcomes and determine whether there are patient subgroups who may benefit from the supplementation. The aim of this IPD meta-analysis is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function.

Methods and analysis

A systematic literature search will be conducted for RCTs of vitamin D supplementation on knee OA. Authors of original RCTs will be contacted to obtain the IPD. The primary outcomes will include long-term ($\geqslant$12 months) pain and physical function. Secondary outcomes will include medium-term ($\geqslant$6 months and <12 months) and short-term (<6 months) pain and physical function, as well as patient global assessment, quality of life and adverse events. Potential treatment effect modifiers to be examined in the subgroup analyses include age, gender, body mass index (BMI), baseline knee pain severity and physical function, baseline vitamin D level, radiographic stage, presence of bone marrow lesions on magnetic resonance images (MRI), presence of clinical signs of local inflammation, and concomitant depressive symptoms. Both one-step and two-step modelling methods will be used to determine the possible modifiable effect of each subgroup of interest.

Ethics and dissemination

Separate ethics committee approval because this study involves analysis of de-identified data that have already been collected in individual RCTs. This study will be the first IPD meta-analysis to clarify the effect of vitamin D supplementation on clinical symptoms in different subgroups of patients with knee OA. The findings will be disseminated through peer-review publications and conference presentations.

Systematic review registration

This systematic review is registered on PROSPERO (CRD42018107740).

Article Summary

This article is a protocol for a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation on joint pain and physical function in patients with symptomatic knee OA.

Strengths and limitations of this study

- This study protocol is endorsed by the OA Trial Bank, an international collaboration that initiates meta-analyses on predefined subgroups of OA patients.
- This study is the first IPD meta-analysis to identify OA patient subgroups that may benefit from vitamin D supplementation.
- IPD meta-analysis offer greater statistical power and precision than subgroup analysis in a single trial and conventional meta-analysis using aggregate data.
- Analysis may be limited to the variables that have been collected across included RCTs.

Introduction

OA is the most common joint disorder worldwide. OA is ranked as the 13th highest contributor of 310 diseases to global disability in 2015[1]. In Australia, OA affects over 2.1 million people (9% of the population), costing the healthcare system over $2.1 billion in 2015[2]. This cost is forecasted to increase by 41% in 2030[3].

The majority (83%) of the disease burden of OA is attributable to knee OA[4], which is characterized by pain, gradual loss of articular cartilage, and structural changes such as subchondral remodelling and effusion-synovitis[5]. Currently, there are no effective disease-modifying treatments to reverse the progression of knee OA once the disease is established. A majority of patients with knee OA eventually progress to advanced stage and undergo total knee replacement[6]. There is clearly an urgent need for innovative and cost-effective approaches to slow the progression of knee OA.

Emerging observational data suggest that vitamin D insufficiency is associated with the onset and progression of knee OA[7]. The association between low serum vitamin D levels and knee OA symptoms may be explained by a direct effect of vitamin D on chondrocytes in osteoarthritic cartilage[8], as well as indirect effects on subchondral bone, synovium, and periarticular muscle[9]. For example, vitamin D deficiency could impair the ability of bone to respond optimally to pathological bone marrow lesions (BMLs) and altered bone mineral density, therefore predisposing the knees to disease progression[10]. Vitamin D also may reduce synovitis in affected knees by regulating cytokine levels in the joint, leading to a reduction in the amount of effusion-synovitis in MRI[11]. In addition, depressive symptoms is interrelated to joint pain in OA[12], and maintaining sufficient serum vitamin D may improve depression symptoms in patients with knee OA[13].

However, evidence from RCTs have been conflicting[14–17]. A pilot RCT in India found a small but statistically significant clinical benefit for 12-month vitamin D treatment on pain and function in patients with knee OA, compared with placebo[3916]. In contrast, a subsequent RCT from the US showed that vitamin D supplementation did not reduce knee pain or cartilage volume loss over 24 months[15]. Subsequently, data from RCTs in Australia[17] and UK[14] did not find significant clinical benefits of vitamin D supplementation for knee OA. However, there was a non-significant trend for symptom reduction (e.g. knee pain and physical function) in these RCTs. Two systematic reviews using aggregate data from these RCTs concluded that, although current evidence does not support vitamin D supplementation for reducing structural disease progression, further research is needed to clarify the effects on patient-reported

outcomes[18,19]. In addition, to the best of our knowledge, no previous systematic reviews of previous systematic reviews exist.

The null results of these RCTs could be due to a low prevalence of vitamin D deficiency in the study subjects or low statistical power secondary to small sample sizes. Another possible reason is that vitamin D may have an effect only in some OA phenotypes, such as those with BMLs (predominant bone abnormality)[20], effusion-synovitis (inflammatory)[21] or depressive symptoms (psychological distress)[13]. Post hoc analyses within these RCTs[47474815,21] were frequently underpowered, and hence unreliable to determine the effect of vitamin D treatment on subgroups of knee OA patients. A meta-analysis using IPD can increase the power of subgroup analysis by combining individual data from included trials[22] and therefore can quantify potential effect modifier of vitamin D treatment in subgroups.

Methods and analysis

We will conduct a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation in patients with symptomatic knee OA. The primary aim is to identify patient-level predictors of treatment response to vitamin D supplementation, including the status of vitamin D deficiency, MRI-detected bone marrow abnormalities and effusion-synovitis, and clinical signs of local inflammation. The protocol of this review is registered on the PROSPERO database (CRD42018107740).

Study eligibility

This systematic review will include studies that meet the following inclusion criteria:

Type of studies

RCTs that have been published in journals and reported the efficacy of vitamin D in participants with knee OA will be included. Cross-over design will also be eligible and only the first phase data will be included in the analysis. Both individually randomised trials and cluster randomised trials will be eligible. Both open-labelled and blinded studies will be eligible. There will be no language or geographical restrictions applied to study selection.

Participants

Men and women who have a diagnosis of knee OA, either according to the American College of Rheumatology criteria, or on the basis of detailed clinical and/or radiographic information, will be included. Studies with a subgroup of knee OA patients will also be included, provided that IPD can be collected separately for the OA subgroup. Although most patients with knee OA defined by the American College of Rheumatology are usually over 50 years of age, the

disease can occur as early as 20 years old, therefore studies with adults at 18 years of age and older will be included.

Interventions

Only studies investigating oral supplementation of vitamin D will be included. Vitamin D treatments administered subcutaneously, intraperitoneally or intravenously will not be included. Both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) will be eligible, irrespective of preparations (tablet or capsule), dosage, regimen, and length of treatment.

Comparators

Oral vitamin D supplementation will be compared with control treatment including placebo or usual conservative care (pain medication and/or exercise therapy if they are used in both treatment and control groups).

Outcomes

The minimum criterion for inclusion is reporting pain or physical function as either primary or secondary outcomes. There will be no restrictions on the duration of follow-up. Data on other outcomes (e.g. patient's global assessment, quality of life, and adverse events) will be analysed when feasible but will not be required for study selection.

Baseline assessments

As a minimum, included studies should have measured knee pain, physical function, serum levels of vitamin D at baseline, and included basic patient characteristics such as age, gender, and BMI.

Literature search

A systematic literature search for articles published from 1 January 1990 until 31 December 2019 will be performed by a trained review author (XJ) in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE;

A previous systematic review[7] has showed that no major RCTs were conducted for vitamin D and osteoarthritis by the year 1990, therefore we chose 1 January 1990 as the start date of the literature search. The search strategies used for each database are listed in *Appendix 1*. All retrieved articles will be exported to the reference manager *EndNote,* in which duplicates will be removed electronically and manually. The remaining records will be exported to an online systematic review management tool *Covidence* (Veritas Health Innovation, Melbourne, Australia) and the articles will be assessed for eligibility for inclusion. In addition to the

electronic search, we will check the reference lists of included trials and previous systematic reviews to identify any trials that are not retrieved from the electronic search. Review authors and collaborating authors will be asked if they are aware of further relevant studies not yet included. We will also search the WHO International Clinical Trial Registration Platform Search Portal (www.who.int/trialsearch) to identify any relevant trials that are completed but did not published the results.

Study selection

Two review authors (XJ, BA) will independently conduct study screening by assessing the article titles and abstracts. Full texts of the articles will be further assessed if the information from the abstract suggests that a study is eligible for inclusion. When information contained in the full text is not sufficient to make a judgement on its eligibility, we will make efforts to contact the corresponding authors to obtain further details. If a corresponding author is not contactable after two email attempts and one phone call, the study will be deemed ineligible. Any disagreement regarding the inclusion of a study will be discussed between the two review authors (XJ, BA). If no consensus can be reached, a third review author will be consulted (XW) to make a final decision.

Extraction of aggregate data

Study data extraction will be performed independently by two review authors (BA, XW). Discrepancies will be resolved by a third reviewer (XJ). We will extract the following study data from the included studies:

- General information: article title, bibliographic details, published language, and funding source.
- Participants: inclusion criteria, exclusion criteria, number of participants in total and in each study arm, study settings, and baseline participant characteristics (e.g. age, gender, BMI).
- Intervention: type of vitamin D preparation, dose, regimen, treatment duration, type of control, and co-interventions (if any).
- Outcomes: primary and secondary outcomes at the end of treatment and/or the end of follow-up. Number of withdrawals and loss to follow-up. Adverse events recorded.
- Data analysis: statistical models used for data analysis, confounding factors adjusted in the models, and methods used for addressing missing values.

Risk of bias assessment

The methodological quality of the included studies will be assessed using a modified version of the Cochrane's risk of bias tool[23]. The modified version includes all the seven domains of the original tool, but further separates performance bias assessment into 'blinding of participants' and 'blinding of study personnel', as well as pre-specifies other sources of bias as 'balance in baseline covariates', 'treatment compliance', and 'timely outcome assessment' (*Appendix 2*). Each domain will be scored as 'low risk', 'high risk' or 'unclear' according to the criteria described in the *Appendix 3*. The overall rating of risk of bias is based on the number of domains with a 'high-risk' score. The overall rating is intended to inform readers of the risk of bias across individual studies and will not be used to weight the studies in the meta-analysis. Two review authors (XJ, XW) will independently evaluate the quality of an individual study. Any disagreement will be settled by further discussion until a consensus is reached between the two review authors.

IPD collection and transfer

The primary or corresponding authors of included trials will be invited to collaborate on the project and contribute their raw data. When we cannot reach a corresponding author after sending two emails and making two telephone calls, we will contact the co-authors listed in the article. If none of the co-authors can be contacted, we will approach the institutes, in which the trial has been conducted. All data custodians will be asked to sign a data delivery agreement, which includes items regarding IPD delivery, obligations, ownership of data, terms and conditions of the use of the data, authorship, and publications. If needed, the project coordinator (XJ) will visit the institutes of the data deliverers to retrieve the data and to sign the data delivery agreement on behalf of the OA Trial Bank (the detailed procedures of data delivery and an example of the data delivery agreement can be found on the OA Trial Bank website https://www.oatrialbank.com/procedures/). De-identified datasets will be accepted in any electronic format (for example, SPSS, Stata, SAS, Excel) or in paper form, provided that variables and categories are adequately labelled within the dataset or within a separate codebook. The IPD files received by the coordinator will be kept in their original version and saved on a secured password-protected server at Erasmus MC Medical University in Rotterdam. The datasets will not be used for any other research apart from that described in the license agreement.

To ensure the quality of the data, the coordinator will independently check for data consistency by comparing the summary statistics derived from the IPD received against the summary

results reported in the published articles. In the case of differences, the project coordinator will communicate with the data deliverer via email or teleconference to resolve the discrepancy.

Variables of interest

The following IPD variables will be obtained (where available):

Primary outcome variables

The primary outcomes for this meta-analysis will be pain and physical function at long-term follow-up (12 months or more). This definition of 'long-term effect' for knee OA treatment was used in previous systematic reviews of knee OA research[24,25].

- Knee pain will be evaluated using visual analogue scale (VAS) if available, otherwise the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[26] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[27] will be used. The pain data will be converted into a 0-100 common scale as recommended by the WOMAC manual[28].
- Physical function will be evaluated using a validated instrument specific to knee OA, such as the physical function subscales of the WOMAC or the KOOS subscales. The scores will be standardised into a 0-100 scale.

Secondary outcome variables

Secondary outcomes will include:

- Medium-term (more than 6 months but less than 12 months) pain and physical function;
- Short-term (less than 6 months) pain and physical function;
- Patient global assessment at the end of study follow-up, as recommended by the OMERACT-OARSI Initiative[29].
- Quality of life evaluated using a validated instrument, such as EQ-5D[30], osteoarthritis Knee and Hip Quality of Life (OAKHQOL)[31], or original instrument used in the included studies;
- Adverse events if reported, including all major and minor events such as hypocalcaemia, fractures, and depression.

Potential treatment effect moderators

If data are available, we will analyse potential treatment effect modification for the following variables measured at baseline:

- Radiographic stage of knee OA (mild/moderate or severe). Radiographic knee OA should be staged at baseline using either the Kellgren-Lawrence (KL)[32] or Osteoarthritis Research

Society International (OARSI) joint space narrowing (JSN) grading system[33]. The results from the two grading systems have been shown to be highly correlated[34]. Mild to moderate disease will be defined as a KL score ≤ 3 or an OARSI JSN score ≤ 2, and severe disease will be a KL score of 4, or an OARSI score of 3.

- Vitamin D level (deficiency, insufficiency, or sufficiency). Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥50 nmol/L is considered as vitamin D sufficiency[35].
- Presence of BMLs (yes or no). BMLs at the patella-femoral and femoro-tibial joints should be measured by MRI using a validated scoring system, such as BLOKS (Boston Leeds Osteoarthritis Knee Score)[36], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[37], or KOSS (Knee Osteoarthritis Scoring System)[38].
- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination - tumor (swelling), dolor (pain), rubor (redness), calor (heat), and functio laesa (disturbance of function) - or by additional laboratory testing (e.g. serum c-reactive protein and erythrocyte sedimentation rate). Effusion-synovitis should be measured on either ultrasound or MRI.
- Presence of depressive symptoms or comorbid depression. Depressive symptoms are measured using a validated questionnaire, such as the Patient Health Questionnaire (PHQ-9)[39] and the Geriatric Depression Scale (GDS)[40].

Data synthesis and statistical methods

All statistical analysis will be conducted using R version 3.5.0 and RStudio (version 1.0.136, RStudio, Inc., Boston, MA), with R extension package 'metafor' for the conventional meta-analysis and two-stage IPD meta-analysis, and 'lme4' for the one-stage IPD meta-analysis.

Conventional meta-analysis

An aggregate data meta-analysis, using a random-effects model based on the 'Hartung-Knapp-Sidik-Jonkman (HKSJ)' method[41], will be performed to estimate the treatment effect of vitamin D over control. If an included study is a cluster RCT, results will be corrected using previously established procedures[42]. The results will be compared with the IPD meta-analysis findings as sensitivity analyses.

Heterogeneity will be assessed by inspecting the forest plots and tested by χ^2 test. A result of $p<0.10$ will be defined as evidence of significant heterogeneity across studies. I^2 test will be

used to estimate the extent of inconsistency across studies that is due to heterogeneity[43]. A result of over 30% and 50% represents moderate and substantial heterogeneity, respectively. Sources of heterogeneity will be explored by excluding individual trials causing an I^2 score below 50%.

If 10 trials or more trials are available, we will use a Doi plot (normal quantile versus effect size plot) explore publication bias and 'small-study effects'[44]. Asymmetry in the Doi plot will be detected and quantified by the LFK index. A value beyond +/- 1 will be deemed consistent with asymmetry, thus having considerable small-study effects[44].

IPD meta-analysis

IPD from included trials will be recoded and formatted in a consistent way to permit re-analysis. A new variable will be created to indicate the trial in which the IPD are collected. The method used to handle missing data will depend on the mechanism causing the missingness. If no explanation is known for the reason of missing data, they will be assumed to be missing at random. We will use the R MICE package[45] for multiple imputation and the imputation model will include all available patient variables to help predict missing data for the variables of interest within each study dataset. The imputation procedure will use 20 imputed datasets. A sensitivity analyses will be performed restricting to participants without missing data (complete case analysis).

Both the treatment effect of vitamin D supplementation and the effect of potential moderators will be studied in the IPD meta-analyses. The treatment effect of vitamin D will be measured using the mean difference in knee pain and physical function between treatment and control based on the intention-to-treat principle. The interaction between the treatment and a potential moderator will be used to identify the effect of the moderator. Interaction effects with $p<0.05$ will be considered statistically significant and 95% confidence intervals of the effects will be provided. The IPD meta-analyses will be undertaken using both the one-stage and two-stage approaches. We will use the one-stage approach as the primary analysis to avoid assumptions of within-study normality and known within-study variance[46]. We will and compare the results to the two-stage approach to assess consistency in a sensitivity analysis.

One-stage modelling

The one-stage mixed-effects IPD meta-analysis approach will take into account both study level and subject-level covariates. Subject -level covariates will be centred to the mean of the covariate in each trial to avoid ecological bias. Three multilevel regression models will be built, the first to examine the summary treatment effect (difference between vitamin D and control),

the second to evaluate each of the mentioned moderators on treatment effect, and the third to assess the true effect of one moderator independent of other moderators.

The first model will include outcome measure (e.g. pain score at follow-up) as a dependent variable, treatment (vitamin D or control), baseline subject-level covariate (e.g. pain score) and confounders (age, gender and BMI) as fixed-effect independent variables, adjusted for study identifier (random intercept). The partial regression coefficient of the treatment will be used to compare to the conventional meta-analysis.

The second model will further add the moderator of interest (e.g. radiographic stage of the disease) and interaction term between the treatment and study-centred values of the moderator in the fixed-effect of the first model. The regression coefficient of the interaction term will be used to quantify the impact of the moderator on treatment effect.

If there are two or more moderators that have a statistically significant interaction with the treatment effect, these moderators will be incorporated in the third model. Multicollinearity between moderators will be tested before building the third model. A correlation coefficient $r>0.80$ will indicate that multiple collinearity exists between the two moderators, of which the one that has less measurement error will be included in the model.

Two-stage modelling

In the first stage, treatment effect and variance are derived from separate analysis in each study. An analysis of covariance (ANCOVA) model adjusted for baseline covariates (age, gender, BMI, as well as knee pain or function), will be used to obtain the treatment effect and variance within each study separately. The effect of a moderator and its variance within each study will be obtained by adding the interaction term between treatment effect and the moderator into the model. In the second stage, the treatment effect and its variances obtained from the first stage will be pooled across studies using a random-effects model[41]. The result of this model is a summary estimate of the treatment effect of vitamin D versus control. The effect of a moderator will be calculated by pooling the regression coefficient and variance of the interaction term between the treatment and the moderator using a similar model. If two or more interaction terms are statistically significant, these moderators will be incorporated in a further model to evaluate the independent effect of these moderators.

Patient and public involvement

We do not directly include patient and public involvement in this study, but the design of included randomised controlled trials may involve patients.

Discussion

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial[7,18]. In a few existing RCTs in patients with symptomatic knee OA[27,14,16,17], small to modest improvement in knee pain and physical function were observed in participants receiving vitamin D supplementation, but the treatment response varies considerably and the effects were not statistically significant when compared to placebo. The broad variation in treatment response could be a result of the fact that knee OA is a highly heterogenous disease with multiple aetiologies[47]. Vitamin D may therefore be more effective in a subset of patients with specific characteristics than others. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short- and long-term follow-up.

Meta-analysis is considered by some to be the grandmother of 'big data'[48] and an integrated part of precision medicine[49]. It is a cost-effective approach to identify potential moderators of treatment response at a patient level, which is not possible with subgroup analyses in a single trial or conventional meta-analysis with aggregate data[50]. Subgroup analyses within individual trials are often underpowered to generate reliable findings. In contrast, IPD meta-analysis techniques increase the statistical power of the study by combining individual observation data from multiple trials with the same treatment[22]. This offers greater precision in analysing moderators of treatment response and offers the potential to analyse a greater number of moderators. In conventional meta-analysis, meta-regression analysis may be used to examine differences in the types of patients enrolled in individual trials, but is potentially problematic. Meta-regression analysis may make incorrect inferences about individual characteristics based upon aggregate baseline statistics reported in trial publications[51]. This is also known as ecological fallacy[52], where the relationship between the effect estimate and average patient characteristics across trials may not be the same as the relationship within individual trials.

Identifying different phenotypes of knee OA is currently a popular subject of research in the field. Different phenotyping strategies have been proposed based on risk factors from epidemiological studies[53], anatomical abnormalities on modern imaging[54], or molecular abnormalities related to pathological mechanisms[55]. While there is currently no standardised classification system for knee OA phenotypes[5], we believe that disease phenotypes are most meaningful when they reflect differential treatment effects. IPD meta-analysis provides an

opportunity to assess the effect of treatments on subtypes or phenotypes of patients with knee OA according to predefined set of characteristics. The current proposed IPD meta-analysis attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

Strengths and limitations

Several challenges may present when conducting an IPD meta-analysis. First, although IPD meta-analyses usually offer sufficient statistical power to examine moderators of treatment response, not all RCTs measure potential moderators of interest or measure them in the same way. This may limit the analysis to only exploring moderators that have been collected across studies. The current protocol attempts to minimise this risk by including moderators that are commonly reported in OA research. In addition, there are expected barriers to accessing data, such as the authors of included trials not being able to be contacted, or the authors losing access to raw data or not choosing to collaborate, may introduce selection bias into the IPD meta-analysis. However, this could be examined in sensitivity analyses by comparing the results to the conventional meta-analysis or be addressed using frameworks that combine IPD and aggregate data in a meta-analysis[56].

The benefits of using IPD meta-analysis techniques greatly outweigh the challenges of using this intensive method. Previous RCTs and systematic reviews have not had sufficient power to thoroughly examine the differential treatment response of vitamin D supplementation in different subsets of patients with knee OA. The results of this project have a high potential to provide important evidence to guide subgroup-specific treatment decisions in clinical practice to improve therapeutic effectiveness.

Status of project

Currently, literature search in the electronic databases has been commenced.

Abbreviations

OA: osteoarthritis; IPD: individual patient data; RCT: randomised controlled trial; BMI: body mass index; MRI: magnetic resonance imaging; BMLs: bone marrow lesions; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International.

Additional Information

Acknowledgement

We acknowledge the University of Sydney China Study Centre for providing short-term travel support to establish international collaboration for this project.

Ethics approval and consent to participate

Research ethical or governance approval is exempt for this study as no new data are being collected.

Availability of data and material

Erasmus MC intends to create a central databank including data from several randomised clinical trials evaluating one or more interventions in patients with osteoarthritis of the knee or hip (the OA Trial Bank) in order to enable researchers to perform meta-analyses on individual patient data to define sub-groups that are specifically responsive to certain treatments. Data request for future research using data deposited in the OA Trial Bank can be directed to https://www.oatrialbank.com/contact/

Authors contributions

All authors were involved in the study design and all will contribute to the interpretation of the results. CD, BA and XJ concepted this study. WZ and MP provided methodological support for statistical analysis. XJ and BA will contact the potential data delivers and will coordinate the project. CD, FC, TM, NA, RNS and SRS will deliver relevant data from their completed trials. SBZ and MM will facilitate legal agreement for data transfer and provide database management at the OA Trial Bank. XJ, BA and XW will perform the study selection, risk of bias assessment, data collection and analysis. All authors contributed to writing of this manuscript and approved the final submission.

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Competing interests statement

The authors declare that they have no competing interests.

Word count

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Appendix 1. Search strategy

Cochrane CENTRAL

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab,kw

#3. (degenerative near/2 arthritis):ti,ab,kw

#4. coxarthrosis:ti,ab,kw

#5. (#1 OR #2 OR #3 OR #4)

#6. MeSH desclriptor vitamin D explode all trees

#7. (vitamin D):ti,ab,kw

#8. (vitamin D2):ti,ab,kw

#9. (vitamin D3):ti,ab,kw

#10. (1-alpha hydroxyvitamin D3):ti,ab,kw

#11. (1-alpha-hydroxy-vitamin D3):ti,ab,kw

#12. (1-alpha hydroxycalciferol):ti,ab,kw

#13. (1-alpha-hydroxy-calciferol):ti,ab,kw

#14. (1,25 dihydroxyvitamin D3):ti,ab,kw

#15. (1,25-dihydroxy-vitamin D3):ti,ab,kw

#16. (1,25 dihydroxycholecalciferol):ti,ab,kw

#17. (1,25-dihydroxycholecalciferol):ti,ab,kw

#18. (25-hydroxycholecalciferol):ti,ab,kw

#19. (25 hydroxycholecalciferol):ti,ab,kw

#20. (25 hydroxyvitamin D):ti,ab,kw

#21. (25-hydroxy-vitamin D):ti,ab,kw

#22. (alfacalcidol):ti,ab,kw

#23. (calcidiol):ti,ab,kw

#24. (calcitriol):ti,ab,kw

#25. (calcifediol):ti,ab,kw

#26. (calciferol):ti,ab,kw

#27. (ergocalciferol):ti,ab,kw

#28. (cholecalciferol):ti,ab,kw

#29. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)

#30. #5 AND #29

MEDLINE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials.sh.
33. random allocation.sh.
34. double blind method.sh.

35. single-blind method.sh.
36. clinical trial.pt.
37. clinical trials.sh.
38. clinical trial.tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
40. placebos.sh.
41. placebo$.tw.
42. random$.tw.
43. Research Design/
44. comparative study.sh.
45. evaluation studies.sh.
46. follow-up studies.sh.
47. prospective studies.sh.
48. control$.tw.
49. prospectiv$.tw.
50. volunteer$.tw.
51. or/30-50
52. (animal not human).mp.
53. 46 not 47
54. 5 and 29 and 53

EMBASE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. random$.tw.
31. factorial$.tw.
32. crossover$.tw.
33. cross over$.tw.
34. cross-over$.tw.

35. placebo$.tw.
36. (doubl$ adj blind$).tw.
37. (singl$ adj blind$).tw.
38. assign$.tw.
39. allocat$.tw.
40. volunteer$.tw.
41. Crossover Procedure/
42. double-blind procedure.tw.
43. Randomized Controlled Trial/
44. Single Blind Procedure/
45. or/30-44
46. (animal/ or nonhuman/) not human/
47. 45 not 46
48. 5 and 29 and 47

Appendix 2. Modified Cochrane's risk of bias tool.

Source of bias[#]	Low risk	High risk	Unclear	Comments
1. Random sequence generation	☐	☐	☐	
2. Allocation concealment	☐	☐	☐	
3. Blinding of participants	☐	☐	☐	
4. Blinding of key study personnel	☐	☐	☐	
5. Blinding of outcome assessment	☐	☐	☐	
6. Incomplete outcome data	☐	☐	☐	
7. Selective outcome reporting	☐	☐	☐	
8. Imbalance in baseline covariates	☐	☐	☐	
9. Treatment compliance	☐	☐	☐	
10. Timing of outcome assessment	☐	☐	☐	
Overall risk of bias	**Low**	**Moderate**	**High**	
	☐	☐	☐	

[#]See *Appendix 2* for criteria for different levels of risk.

Appendix 3. Criteria for risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Sequence generation process involves judgement or some method of non-random categorisation of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of "High risk":

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2
Authors					
Contact	3a	Provide name, institutional affiliation, and 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 15
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	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 5
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	☒	☐	Page 5, Appendix 1.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8-10
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 8-9
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 7, Appendix 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-12
	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 (e.g., I^2, Kendall's tau)	☒	☐	Page 10-12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	N/A

BMJ Open

The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA) An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

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Primary Subject Heading:	Rheumatology
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Keywords:	PREVENTIVE MEDICINE, RHEUMATOLOGY, GENERAL MEDICINE (see Internal Medicine)

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The Effect of Vitamin D Supplementation on Pain and Physical Function in Patients with Knee Osteoarthritis (OA)

An OA Trial Bank protocol for a systematic review and individual patient data (IPD) meta-analysis

Xingzhong Jin[1,2], Benny Antony[3], Xia Wang[4], Monica SM Persson[5,6], Timothy McAlindon[7], Nigel Arden[8], Sudeepti Ratan Srivastava[9], Rajeshwar Nath Srivastava[9], Marienke van Middelkoop[10], Sita M.A. Bierma-Zeinstra[10], Weiya Zhang[5,6], Flavia Cicuttini[11], Changhai Ding[1,3,11].

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Keywords

Systematic Review; Meta-analysis; Individual Patient Data; Osteoarthritis; Vitamin D; Knee.

Abstract

Introduction

Observational data suggest vitamin D deficiency is associated with the onset and progression of knee OA. However, randomized controlled trials (RCTs) to date investigating the efficacy of vitamin D supplementation in knee OA have reported conflicting results. Further research is needed to clarify the effects of vitamin D on patient-reported outcomes and determine whether there are patient subgroups who may benefit from the supplementation. The aim of this IPD meta-analysis is to identify patient-level predictors of treatment response to vitamin D supplementation on pain and physical function.

Methods and analysis

A systematic literature search will be conducted for RCTs of vitamin D supplementation on knee OA. Authors of original RCTs will be contacted to obtain the IPD. The primary outcomes will include long-term ($\geqslant$12 months) pain and physical function. Secondary outcomes will include medium-term ($\geqslant$6 months and <12 months) and short-term (<6 months) pain and physical function, as well as patient global assessment, quality of life and adverse events. Potential treatment effect modifiers to be examined in the subgroup analyses include age, gender, body mass index (BMI), baseline knee pain severity and physical function, baseline vitamin D level, radiographic stage, presence of bone marrow lesions on magnetic resonance images (MRI), presence of clinical signs of local inflammation, and concomitant depressive symptoms. Both one-step and two-step modelling methods will be used to determine the possible modifiable effect of each subgroup of interest.

Ethics and dissemination

Research ethical or governance approval is exempt for this study as no new data are being collected. This study will be the first IPD meta-analysis to clarify the effect of vitamin D supplementation on clinical symptoms in different subgroups of patients with knee OA. The findings will be disseminated through peer-review publications and conference presentations.

Systematic review registration

This systematic review is registered on PROSPERO (CRD42018107740).

Strengths and limitations of this study

- This study protocol is endorsed by the OA Trial Bank, an international collaboration that initiates meta-analyses on predefined subgroups of OA patients.
- This study is the first IPD meta-analysis to identify OA patient subgroups that may benefit from vitamin D supplementation.
- IPD meta-analysis offer greater statistical power and precision than subgroup analysis in a single trial and conventional meta-analysis using aggregate data.
- Analysis may be limited to the variables that have been collected across included RCTs.

Introduction

OA is the most common joint disorder worldwide. OA is ranked as the 13th highest contributor of 310 diseases to global disability in 2015[1]. In Australia, OA affects over 2.1 million people (9% of the population), costing the healthcare system over $2.1 billion in 2015[2]. This cost is forecasted to increase by 41% in 2030[3].

The majority (83%) of the disease burden of OA is attributable to knee OA[4], which is characterized by pain, gradual loss of articular cartilage, and structural changes such as subchondral remodelling and effusion-synovitis[5]. Currently, there are no effective disease-modifying treatments to reverse the progression of knee OA once the disease is established. A majority of patients with knee OA eventually progress to advanced stage and undergo total knee replacement[6]. There is clearly an urgent need for innovative and cost-effective approaches to slow the progression of knee OA.

Emerging observational data suggest that vitamin D insufficiency is associated with the onset and progression of knee OA[7]. The association between low serum vitamin D levels and knee OA symptoms may be explained by a direct effect of vitamin D on chondrocytes in osteoarthritic cartilage[8], as well as indirect effects on subchondral bone, synovium, and periarticular muscle[9]. For example, vitamin D deficiency could impair the ability of bone to respond optimally to pathological bone marrow lesions (BMLs) and altered bone mineral density, therefore predisposing the knees to disease progression[10]. Vitamin D also may reduce synovitis in affected knees by regulating cytokine levels in the joint, leading to a reduction in the amount of effusion-synovitis in MRI[11]. In addition, depressive symptoms is interrelated to joint pain in OA[12], and maintaining sufficient serum vitamin D may improve depression symptoms in patients with knee OA[13].

However, evidence from RCTs have been conflicting[14–17]. A pilot RCT in India found a small but statistically significant clinical benefit for 12-month vitamin D treatment on pain and function in patients with knee OA, compared with placebo[16]. In contrast, a subsequent RCT from the US showed that vitamin D supplementation did not reduce knee pain or cartilage volume loss over 24 months[15]. Subsequently, data from RCTs in Australia[17] and UK[14] did not find significant clinical benefits of vitamin D supplementation for knee OA. However, there was a non-significant trend for symptom reduction (e.g. knee pain and physical function) in these RCTs. Two systematic reviews using aggregate data from these RCTs concluded that, although current evidence does not support vitamin D supplementation for reducing structural disease progression, further research is needed to clarify the effects on patient-reported

outcomes[18,19]. In addition, to the best of our knowledge, no previous systematic reviews of previous systematic reviews exist.

The null results of these RCTs could be due to a low prevalence of vitamin D deficiency in the study subjects or low statistical power secondary to small sample sizes. Another possible reason is that vitamin D may have an effect only in some OA phenotypes, such as those with BMLs (predominant bone abnormality)[20], effusion-synovitis (inflammatory)[21] or depressive symptoms (psychological distress)[13]. Post hoc analyses within these RCTs[15,21] were frequently underpowered, and hence unreliable to determine the effect of vitamin D treatment on subgroups of knee OA patients. A meta-analysis using IPD can increase the power of subgroup analysis by combining individual data from included trials[22] and therefore can quantify potential effect modifier of vitamin D treatment in subgroups.

Methods and analysis

We will conduct a systematic review and IPD meta-analysis of RCTs studying the effects of vitamin D supplementation in patients with symptomatic knee OA. The primary aim is to identify patient-level predictors of treatment response to vitamin D supplementation, including the status of vitamin D deficiency, MRI-detected bone marrow abnormalities and effusion-synovitis, and clinical signs of local inflammation. The protocol of this review is registered on the PROSPERO database (CRD42018107740).

Study eligibility

This systematic review will include studies that meet the following inclusion criteria:

Type of studies

RCTs that have been published in journals and reported the efficacy of vitamin D in participants with knee OA will be included. Cross-over design will also be eligible and only the first phase data will be included in the analysis. Both individually randomised trials and cluster randomised trials will be eligible. Both open-labelled and blinded studies will be eligible. There will be no language or geographical restrictions applied to study selection.

Participants

Men and women who have a diagnosis of knee OA, either according to the American College of Rheumatology criteria, or on the basis of detailed clinical and/or radiographic information, will be included. Studies with a subgroup of knee OA patients will also be included, provided that IPD can be collected separately for the OA subgroup. Although most patients with knee OA defined by the American College of Rheumatology are usually over 50 years of age, the

disease can occur as early as 20 years old, therefore studies with adults at 18 years of age and older will be included.

Interventions

Only studies investigating oral supplementation of vitamin D will be included. Vitamin D treatments administered subcutaneously, intraperitoneally or intravenously will not be included. Both ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3) will be eligible, irrespective of preparations (tablet or capsule), dosage, regimen, and length of treatment.

Comparators

Oral vitamin D supplementation will be compared with control treatment including placebo or usual conservative care (pain medication and/or exercise therapy if they are used in both treatment and control groups).

Outcomes

The minimum criterion for inclusion is reporting pain or physical function as either primary or secondary outcomes. There will be no restrictions on the duration of follow-up. Data on other outcomes (e.g. patient's global assessment, quality of life, and adverse events) will be analysed when feasible but will not be required for study selection.

Baseline assessments

As a minimum, included studies should have measured knee pain, physical function, serum levels of vitamin D at baseline, and included basic patient characteristics such as age, gender, and BMI.

Literature search

A systematic literature search for articles published from 1 January 1990 until 31 December 2019 will be performed by a trained review author (XJ) in the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (Ovid);
- EMBASE;

A previous systematic review[7] has showed that no major RCTs were conducted for vitamin D and osteoarthritis by the year 1990, therefore we chose 1 January 1990 as the start date of the literature search. The search strategies used for each database are listed in *Appendix 1*. All retrieved articles will be exported to the reference manager *EndNote,* in which duplicates will be removed electronically and manually. The remaining records will be exported to an online systematic review management tool *Covidence* (Veritas Health Innovation, Melbourne, Australia) and the articles will be assessed for eligibility for inclusion. In addition to the

electronic search, we will check the reference lists of included trials and previous systematic reviews to identify any trials that are not retrieved from the electronic search. Review authors and collaborating authors will be asked if they are aware of further relevant studies not yet included. We will also search the WHO International Clinical Trial Registration Platform Search Portal (www.who.int/trialsearch) to identify any relevant trials that are completed but did not published the results.

Study selection

Two review authors (XJ, BA) will independently conduct study screening by assessing the article titles and abstracts. Full texts of the articles will be further assessed if the information from the abstract suggests that a study is eligible for inclusion. When information contained in the full text is not sufficient to make a judgement on its eligibility, we will make efforts to contact the corresponding authors to obtain further details. If a corresponding author is not contactable after two email attempts and one phone call, the study will be deemed ineligible. Any disagreement regarding the inclusion of a study will be discussed between the two review authors (XJ, BA). If no consensus can be reached, a third review author will be consulted (XW) to make a final decision.

Extraction of aggregate data

Study data extraction will be performed independently by two review authors (BA, XW). Discrepancies will be resolved by a third reviewer (XJ). We will extract the following study data from the included studies:

- General information: article title, bibliographic details, published language, and funding source.
- Participants: inclusion criteria, exclusion criteria, number of participants in total and in each study arm, study settings, and baseline participant characteristics (e.g. age, gender, BMI).
- Intervention: type of vitamin D preparation, dose, regimen, treatment duration, type of control, and co-interventions (if any).
- Outcomes: primary and secondary outcomes at the end of treatment and/or the end of follow-up. Number of withdrawals and loss to follow-up. Adverse events recorded.
- Data analysis: statistical models used for data analysis, confounding factors adjusted in the models, and methods used for addressing missing values.

Risk of bias assessment

The methodological quality of the included studies will be assessed using a modified version of the Cochrane's risk of bias tool[23]. The modified version includes all the seven domains of the original tool, but further separates performance bias assessment into 'blinding of participants' and 'blinding of study personnel', as well as pre-specifies other sources of bias as 'balance in baseline covariates', 'treatment compliance', and 'timely outcome assessment' (*Appendix 2*). Each domain will be scored as 'low risk', 'high risk' or 'unclear' according to the criteria described in the *Appendix 3*. The overall rating of risk of bias is based on the number of domains with a 'high-risk' score. The overall rating is intended to inform readers of the risk of bias across individual studies and will not be used to weight the studies in the meta-analysis. Two review authors (XJ, XW) will independently evaluate the quality of an individual study. Any disagreement will be settled by further discussion until a consensus is reached between the two review authors.

IPD collection and transfer

The primary or corresponding authors of included trials will be invited to collaborate on the project and contribute their raw data. When we cannot reach a corresponding author after sending two emails and making two telephone calls, we will contact the co-authors listed in the article. If none of the co-authors can be contacted, we will approach the institutes, in which the trial has been conducted. All data custodians will be asked to sign a data delivery agreement, which includes items regarding IPD delivery, obligations, ownership of data, terms and conditions of the use of the data, authorship, and publications. If needed, the project coordinator (XJ) will visit the institutes of the data deliverers to retrieve the data and to sign the data delivery agreement on behalf of the OA Trial Bank (the detailed procedures of data delivery and an example of the data delivery agreement can be found on the OA Trial Bank website https://www.oatrialbank.com/procedures/). De-identified datasets will be accepted in any electronic format (for example, SPSS, Stata, SAS, Excel) or in paper form, provided that variables and categories are adequately labelled within the dataset or within a separate codebook. The IPD files received by the coordinator will be kept in their original version and saved on a secured password-protected server at Erasmus MC Medical University in Rotterdam. The datasets will not be used for any other research apart from that described in the license agreement.

To ensure the quality of the data, the coordinator will independently check for data consistency by comparing the summary statistics derived from the IPD received against the summary

results reported in the published articles. In the case of differences, the project coordinator will communicate with the data deliverer via email or teleconference to resolve the discrepancy.

Variables of interest

The following IPD variables will be obtained (where available):

Primary outcome variables

The primary outcomes for this meta-analysis will be pain and physical function at long-term follow-up (12 months or more). This definition of 'long-term effect' for knee OA treatment was used in previous systematic reviews of knee OA research[24,25].

- Knee pain will be evaluated using visual analogue scale (VAS) if available, otherwise the pain subscales of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[26] or the Knee injury and Osteoarthritis Outcome Score (KOOS)[27] will be used. The pain data will be converted into a 0-100 common scale as recommended by the WOMAC manual[28].
- Physical function will be evaluated using a validated instrument specific to knee OA, such as the physical function subscales of the WOMAC or the KOOS subscales. The scores will be standardised into a 0-100 scale.

Secondary outcome variables

Secondary outcomes will include:

- Medium-term (more than 6 months but less than 12 months) pain and physical function;
- Short-term (less than 6 months) pain and physical function;
- Patient global assessment at the end of study follow-up, as recommended by the OMERACT-OARSI Initiative[29].
- Quality of life evaluated using a validated instrument, such as EQ-5D[30], osteoarthritis Knee and Hip Quality of Life (OAKHQOL)[31], or original instrument used in the included studies;
- Adverse events if reported, including all major and minor events such as hypocalcaemia, fractures, and depression.

Potential treatment effect moderators

If data are available, we will analyse potential treatment effect modification for the following variables measured at baseline:

- Radiographic stage of knee OA (mild/moderate or severe). Radiographic knee OA should be staged at baseline using either the Kellgren-Lawrence (KL)[32] or Osteoarthritis Research

Society International (OARSI) joint space narrowing (JSN) grading system[33]. The results from the two grading systems have been shown to be highly correlated[34]. Mild to moderate disease will be defined as a KL score ≤ 3 or an OARSI JSN score ≤ 2, and severe disease will be a KL score of 4, or an OARSI score of 3.

- Vitamin D level (deficiency, insufficiency, or sufficiency). Vitamin D deficiency is defined as serum levels of 25(OH)D less than 30 nmol/L at baseline. Insufficiency is defined as serum 25(OH)D levels from 30 to <50 nmol/L. Serum 25(OH)D levels ≥50 nmol/L is considered as vitamin D sufficiency[35].
- Presence of BMLs (yes or no). BMLs at the patella-femoral and femoro-tibial joints should be measured by MRI using a validated scoring system, such as BLOKS (Boston Leeds Osteoarthritis Knee Score)[36], WORMS (Whole-Organ Magnetic Resonance Imaging Score)[37], or KOSS (Knee Osteoarthritis Scoring System)[38].
- Clinical signs of local inflammation or the presence of effusion-synovitis (yes or no). Clinical signs of local inflammation should be assessed by physical examination - tumor (swelling), dolor (pain), rubor (redness), calor (heat), and functio laesa (disturbance of function) - or by additional laboratory testing (e.g. serum c-reactive protein and erythrocyte sedimentation rate). Effusion-synovitis should be measured on either ultrasound or MRI.
- Presence of depressive symptoms or comorbid depression. Depressive symptoms are measured using a validated questionnaire, such as the Patient Health Questionnaire (PHQ-9)[39] and the Geriatric Depression Scale (GDS)[40].

Data synthesis and statistical methods

All statistical analysis will be conducted using R version 3.5.0 and RStudio (version 1.0.136, RStudio, Inc., Boston, MA), with R extension package 'metafor' for the conventional meta-analysis and two-stage IPD meta-analysis, and 'lme4' for the one-stage IPD meta-analysis.

Conventional meta-analysis

An aggregate data meta-analysis, using a random-effects model based on the 'Hartung-Knapp-Sidik-Jonkman (HKSJ)' method[41], will be performed to estimate the treatment effect of vitamin D over control. If an included study is a cluster RCT, results will be corrected using previously established procedures[42]. The results will be compared with the IPD meta-analysis findings as sensitivity analyses.

Heterogeneity will be assessed by inspecting the forest plots and tested by χ^2 test. A result of $p<0.10$ will be defined as evidence of significant heterogeneity across studies. I^2 test will be

used to estimate the extent of inconsistency across studies that is due to heterogeneity[43]. A result of over 30% and 50% represents moderate and substantial heterogeneity, respectively. Sources of heterogeneity will be explored by excluding individual trials causing an I^2 score below 50%.

If 10 trials or more trials are available, we will use a Doi plot (normal quantile versus effect size plot) explore publication bias and 'small-study effects'[44]. Asymmetry in the Doi plot will be detected and quantified by the LFK index. A value beyond +/- 1 will be deemed consistent with asymmetry, thus having considerable small-study effects[44].

IPD meta-analysis

IPD from included trials will be recoded and formatted in a consistent way to permit re-analysis. A new variable will be created to indicate the trial in which the IPD are collected. The method used to handle missing data will depend on the mechanism causing the missingness. If no explanation is known for the reason of missing data, they will be assumed to be missing at random. We will use the R MICE package[45] for multiple imputation and the imputation model will include all available patient variables to help predict missing data for the variables of interest within each study dataset. The imputation procedure will use 20 imputed datasets. A sensitivity analyses will be performed restricting to participants without missing data (complete case analysis).

Both the treatment effect of vitamin D supplementation and the effect of potential moderators will be studied in the IPD meta-analyses. The treatment effect of vitamin D will be measured using the mean difference in knee pain and physical function between treatment and control based on the intention-to-treat principle. The interaction between the treatment and a potential moderator will be used to identify the effect of the moderator. Interaction effects with $p<0.05$ will be considered statistically significant and 95% confidence intervals of the effects will be provided. The IPD meta-analyses will be undertaken using both the one-stage and two-stage approaches. We will use the one-stage approach as the primary analysis to avoid assumptions of within-study normality and known within-study variance[46]. We will and compare the results to the two-stage approach to assess consistency in a sensitivity analysis.

One-stage modelling

The one-stage mixed-effects IPD meta-analysis approach will take into account both study level and subject-level covariates. Subject -level covariates will be centred to the mean of the covariate in each trial to avoid ecological bias. Three multilevel regression models will be built, the first to examine the summary treatment effect (difference between vitamin D and control),

the second to evaluate each of the mentioned moderators on treatment effect, and the third to assess the true effect of one moderator independent of other moderators.

The first model will include outcome measure (e.g. pain score at follow-up) as a dependent variable, treatment (vitamin D or control), baseline subject-level covariate (e.g. pain score) and confounders (age, gender and BMI) as fixed-effect independent variables, adjusted for study identifier (random intercept). The partial regression coefficient of the treatment will be used to compare to the conventional meta-analysis.

The second model will further add the moderator of interest (e.g. radiographic stage of the disease) and interaction term between the treatment and study-centred values of the moderator in the fixed-effect of the first model. The regression coefficient of the interaction term will be used to quantify the impact of the moderator on treatment effect.

If there are two or more moderators that have a statistically significant interaction with the treatment effect, these moderators will be incorporated in the third model. Multicollinearity between moderators will be tested before building the third model. A correlation coefficient $r>0.80$ will indicate that multiple collinearity exists between the two moderators, of which the one that has less measurement error will be included in the model.

Two-stage modelling

In the first stage, treatment effect and variance are derived from separate analysis in each study. An analysis of covariance (ANCOVA) model adjusted for baseline covariates (age, gender, BMI, as well as knee pain or function), will be used to obtain the treatment effect and variance within each study separately. The effect of a moderator and its variance within each study will be obtained by adding the interaction term between treatment effect and the moderator into the model. In the second stage, the treatment effect and its variances obtained from the first stage will be pooled across studies using a random-effects model[41]. The result of this model is a summary estimate of the treatment effect of vitamin D versus control. The effect of a moderator will be calculated by pooling the regression coefficient and variance of the interaction term between the treatment and the moderator using a similar model. If two or more interaction terms are statistically significant, these moderators will be incorporated in a further model to evaluate the independent effect of these moderators.

Patient and public involvement

We do not directly include patient and public involvement in this study, but the design of included randomised controlled trials may involve patients.

Discussion

Vitamin D supplementation may improve pain and function in patients with knee OA; however, the evidence from observational studies and RCTs are controversial[7,18]. In a few existing RCTs in patients with symptomatic knee OA[14,16,17], small to modest improvement in knee pain and physical function were observed in participants receiving vitamin D supplementation, but the treatment response varies considerably and the effects were not statistically significant when compared to placebo. The broad variation in treatment response could be a result of the fact that knee OA is a highly heterogenous disease with multiple aetiologies[47]. Vitamin D may therefore be more effective in a subset of patients with specific characteristics than others. The purpose of the proposed IPD meta-analysis is to evaluate the treatment response of vitamin D supplementation on pain and physical function for knee OA in specific subsets of patients according to disease severity, vitamin D levels, presence of BMLs, inflammatory signs and depressive symptoms, over both short- and long-term follow-up.

Meta-analysis is considered by some to be the grandmother of 'big data'[48] and an integrated part of precision medicine[49]. It is a cost-effective approach to identify potential moderators of treatment response at a patient level, which is not possible with subgroup analyses in a single trial or conventional meta-analysis with aggregate data[50]. Subgroup analyses within individual trials are often underpowered to generate reliable findings. In contrast, IPD meta-analysis techniques increase the statistical power of the study by combining individual observation data from multiple trials with the same treatment[22]. This offers greater precision in analysing moderators of treatment response and offers the potential to analyse a greater number of moderators. In conventional meta-analysis, meta-regression analysis may be used to examine differences in the types of patients enrolled in individual trials, but is potentially problematic. Meta-regression analysis may make incorrect inferences about individual characteristics based upon aggregate baseline statistics reported in trial publications[51]. This is also known as ecological fallacy[52], where the relationship between the effect estimate and average patient characteristics across trials may not be the same as the relationship within individual trials.

Identifying different phenotypes of knee OA is currently a popular subject of research in the field. Different phenotyping strategies have been proposed based on risk factors from epidemiological studies[53], anatomical abnormalities on modern imaging[54], or molecular abnormalities related to pathological mechanisms[55]. While there is currently no standardised classification system for knee OA phenotypes[5], we believe that disease phenotypes are most meaningful when they reflect differential treatment effects. IPD meta-analysis provides an

opportunity to assess the effect of treatments on subtypes or phenotypes of patients with knee OA according to predefined set of characteristics. The current proposed IPD meta-analysis attempts to differentiate subgroups by identifying subtypes of patients that respond better to vitamin D supplementation on pain and physical function.

Strengths and limitations

Several challenges may present when conducting an IPD meta-analysis. First, although IPD meta-analyses usually offer sufficient statistical power to examine moderators of treatment response, not all RCTs measure potential moderators of interest or measure them in the same way. This may limit the analysis to only exploring moderators that have been collected across studies. The current protocol attempts to minimise this risk by including moderators that are commonly reported in OA research. In addition, there are expected barriers to accessing data, such as the authors of included trials not being able to be contacted, or the authors losing access to raw data or not choosing to collaborate, may introduce selection bias into the IPD meta-analysis. However, this could be examined in sensitivity analyses by comparing the results to the conventional meta-analysis or be addressed using frameworks that combine IPD and aggregate data in a meta-analysis[56].

The benefits of using IPD meta-analysis techniques greatly outweigh the challenges of using this intensive method. Previous RCTs and systematic reviews have not had sufficient power to thoroughly examine the differential treatment response of vitamin D supplementation in different subsets of patients with knee OA. The results of this project have a high potential to provide important evidence to guide subgroup-specific treatment decisions in clinical practice to improve therapeutic effectiveness.

Status of project

Currently, literature search in the electronic databases has been commenced.

Abbreviations

OA: osteoarthritis; IPD: individual patient data; RCT: randomised controlled trial; BMI: body mass index; MRI: magnetic resonance imaging; BMLs: bone marrow lesions; JSN: joint space narrowing; OARSI: Osteoarthritis Research Society International.

Additional Information

Acknowledgement

We acknowledge the University of Sydney China Study Centre for providing short-term travel support to establish international collaboration for this project.

Ethics approval and consent to participate

Research ethical or governance approval is exempt for this study as no new data are being collected.

Availability of data and material

Erasmus MC intends to create a central databank including data from several randomised clinical trials evaluating one or more interventions in patients with osteoarthritis of the knee or hip (the OA Trial Bank) in order to enable researchers to perform meta-analyses on individual patient data to define sub-groups that are specifically responsive to certain treatments. Data request for future research using data deposited in the OA Trial Bank can be directed to https://www.oatrialbank.com/contact/

Authors contributions

All authors were involved in the study design and all will contribute to the interpretation of the results. CD, BA and XJ concepted this study. WZ and MP provided methodological support for statistical analysis. XJ and BA will contact the potential data delivers and will coordinate the project. CD, FC, TM, NA, RNS and SRS will deliver relevant data from their completed trials. SBZ and MM will facilitate legal agreement for data transfer and provide database management at the OA Trial Bank. XJ, BA and XW will perform the study selection, risk of bias assessment, data collection and analysis. All authors contributed to writing of this manuscript and approved the final submission.

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Competing interests statement

The authors declare that they have no competing interests.

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Appendix 1. Search strategy

Cochrane CENTRAL

#1. MeSH descriptor Osteoarthritis explode all trees

#2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*):ti,ab,kw

#3. (degenerative near/2 arthritis):ti,ab,kw

#4. coxarthrosis:ti,ab,kw

#5. (#1 OR #2 OR #3 OR #4)

#6. MeSH desclriptor vitamin D explode all trees

#7. (vitamin D):ti,ab,kw

#8. (vitamin D2):ti,ab,kw

#9. (vitamin D3):ti,ab,kw

#10. (1-alpha hydroxyvitamin D3):ti,ab,kw

#11. (1-alpha-hydroxy-vitamin D3):ti,ab,kw

#12. (1-alpha hydroxycalciferol):ti,ab,kw

#13. (1-alpha-hydroxy-calciferol):ti,ab,kw

#14. (1,25 dihydroxyvitamin D3):ti,ab,kw

#15. (1,25-dihydroxy-vitamin D3):ti,ab,kw

#16. (1,25 dihydroxycholecalciferol):ti,ab,kw

#17. (1,25-dihydroxycholecalciferol):ti,ab,kw

#18. (25-hydroxycholecalciferol):ti,ab,kw

#19. (25 hydroxycholecalciferol):ti,ab,kw

#20. (25 hydroxyvitamin D):ti,ab,kw

#21. (25-hydroxy-vitamin D):ti,ab,kw

#22. (alfacalcidol):ti,ab,kw

#23. (calcidiol):ti,ab,kw

#24. (calcitriol):ti,ab,kw

#25. (calcifediol):ti,ab,kw

#26. (calciferol):ti,ab,kw

#27. (ergocalciferol):ti,ab,kw

#28. (cholecalciferol):ti,ab,kw

#29. (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28)

#30. #5 AND #29

MEDLINE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomized controlled trials.sh.
33. random allocation.sh.
34. double blind method.sh.

35. single-blind method.sh.
36. clinical trial.pt.
37. clinical trials.sh.
38. clinical trial.tw.
39. ((singl$ or doubl$ or trebl$ or tripl$) and (mask$ or blind$)).tw.
40. placebos.sh.
41. placebo$.tw.
42. random$.tw.
43. Research Design/
44. comparative study.sh.
45. evaluation studies.sh.
46. follow-up studies.sh.
47. prospective studies.sh.
48. control$.tw.
49. prospectiv$.tw.
50. volunteer$.tw.
51. or/30-50
52. (animal not human).mp.
53. 46 not 47
54. 5 and 29 and 53

EMBASE (via Ovid)

1. exp osteoarthritis/
2. (osteoarthriti* or osteo-arthriti* or osteoarthrotic or osteoarthros*).ti,ab.
3. (degenerative adj2 arthritis).ti,ab.
4. coxarthrosis.ti,ab.
5. or/1-4
6. exp Vitamin D/
7. vitamin D.tw.
8. vitamin D2.tw.
9. vitamin D3.tw.
10. 1-alpha hydroxyvitamin D3.tw.
11. 1-alpha-hydroxy-vitamin D3.tw.
12. 1-alpha hydroxycalciferol.tw.
13. 1-alpha-hydroxy-calciferol.tw.
14. 1,25 dihydroxyvitamin D3.tw.
15. 1,25-dihydroxy-vitamin D3.tw.
16. 1,25 dihydroxycholecalciferol.tw.
17. 1,25-dihydroxycholecalciferol.tw.
18. 25-hydroxycholecalciferol.tw.
19. 25 hydroxycholecalciferol.tw.
20. 25 hydroxyvitamin D.tw.
21. 25-hydroxy-vitamin D.tw.
22. alfacalcidol.tw.
23. calcidiol.tw.
24. calcitriol.tw.
25. calcifediol.tw.
26. calciferol.tw.
27. ergocalciferol.tw.
28. cholecalciferol.tw.
29. or/6-28
30. random$.tw.
31. factorial$.tw.
32. crossover$.tw.
33. cross over$.tw.
34. cross-over$.tw.

35. placebo$.tw.
36. (doubl$ adj blind$).tw.
37. (singl$ adj blind$).tw.
38. assign$.tw.
39. allocat$.tw.
40. volunteer$.tw.
41. Crossover Procedure/
42. double-blind procedure.tw.
43. Randomized Controlled Trial/
44. Single Blind Procedure/
45. or/30-44
46. (animal/ or nonhuman/) not human/
47. 45 not 46
48. 5 and 29 and 47

Appendix 2. Modified Cochrane's risk of bias tool.

Source of bias[#]	Low risk	High risk	Unclear	Comments
1. Random sequence generation	☐	☐	☐	
2. Allocation concealment	☐	☐	☐	
3. Blinding of participants	☐	☐	☐	
4. Blinding of key study personnel	☐	☐	☐	
5. Blinding of outcome assessment	☐	☐	☐	
6. Incomplete outcome data	☐	☐	☐	
7. Selective outcome reporting	☐	☐	☐	
8. Imbalance in baseline covariates	☐	☐	☐	
9. Treatment compliance	☐	☐	☐	
10. Timing of outcome assessment	☐	☐	☐	
Overall risk of bias	**Low**	**Moderate**	**High**	
	☐	☐	☐	

[#]See *Appendix 2* for criteria for different levels of risk.

Appendix 3. Criteria for risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

The investigators describe a random component in the sequence generation process such as:

- Referring to a random number table;
- Using a computer random number generator;
- Coin tossing;
- Shuffling cards or envelopes;
- Throwing dice;
- Drawing of lots;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves some systematic, non-random approach, for example:

- sequence generated by odd or even date of birth;
- sequence generated by some rule based on date (or day) of admission;
- sequence generated by some rule based on hospital or clinic record number.

Sequence generation process involves judgement or some method of non-random categorisation of participants, for example:

- Allocation by judgement of the clinician;
- Allocation by preference of the participant;
- Allocation based on the results of a laboratory test or a series of tests;
- Allocation by availability of the intervention.

Criteria for a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- Using an open random allocation schedule (e.g. a list of random numbers);
- Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- Alternation or rotation;
- Date of birth;
- Case record number;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;
- Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment is likely to be influenced by lack of blinding;
- Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Criteria for a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for a judgement of "High risk":

Any one of the following:

- Not all of the study's pre-specified primary outcomes have been reported;
- One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;
- One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - **Moher D, Stewart L & Shekelle P:** Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
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	☐	☒	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Page 2
Authors					
Contact	3a	Provide name, institutional affiliation, and 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 15
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	☐	☒	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	Page 15
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	Page 15
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	Page 15
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	Page 4-5

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	Page 5
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	Page 6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	Page 5
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	☒	☐	Page 5, Appendix 1.
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	Page 7-8
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	Page 6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	Page 8
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	Page 8-10
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 8-9
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 7, Appendix 2
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	Page 10-12
	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 (e.g., I^2, Kendall's tau)	☒	☐	Page 10-12
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	N/A

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	N/A