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Vitamin D supplementation and energy and metabolic homeostasis in obese and overweight subjects: a protocol for a systematic review

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Key words: vitamin D; obesity and overweight; energy homeostasis; metabolic homeostasis; systematic review; protocol

ABSTRACT

Introduction Obesity and vitamin D deficiency are both major public health problems. According to the pathophysiological mechanism of obesity as well as the bidirectional relationship between obesity and vitamin D metabolism and storage, vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Objectives Our review will assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

Methods and analysis In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), we will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to the date of the searches. A manual search of the reference lists of all relevant research articles will be performed to identify additional studies. We will include randomized controlled trials published in English examining effects of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. Two reviewers will independently complete the article selection, data extraction and rating. The bias tool from the Cochrane Handbook for Systematic Reviews of Interventions will be used to assess the methodological quality of the included studies. Narrative or quantitative synthesis will be done depending on the available data.

Ethics and dissemination Ethical approval will not be required for this review. The

results of this review will be disseminated in a peer-review journal.

Registration details PROSPERO International prospective register of systematic reviews registration number: CRD42021228981.

Strengths and limitations of this study

This review protocol provides an overview of the current situation in both major public health problems: obesity and vitamin D deficiency.

The bidirectional relationship between obesity and vitamin D metabolism and storage informs the development of a systematic review of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

This study will potentially be helpful to provide a valuable reference for future evidence-based as well as fundamental research to refine vitamin D supplementation in clinical practice and public health.

INTRODUCTION

The definition of overweight and obesity is abnormal or excessive fat accumulation that may impair health.[1] With the continued increasing of prevalence across the world, overweight and obesity has been described as a global pandemic.[2-5] Since 1975, the prevalence of obesity worldwide has nearly tripled.[1] In 2016, over a third of adults worldwide were overweight and 13% were obese;[1, 6] over 340 million children and adolescents aged above 5 were overweight or obese.[1, 6] If this trend continues, it has been projected that up to 57.8% of the world's adult population could be either

overweight or obese by 2030.[7] The high prevalence of overweight and obesity, combined with the associated disease burden as well as higher all-cause mortality, makes it a global public health challenge.[8, 9] Moreover, the disease burden of overweight and obesity has been greatly magnified by the current COVID-19 pandemic, as overweight and obesity were represented an unfavorable factor for COVID-19 severity and mortality.[10-12]

Vitamin D deficiency is another important public health issue, which often coexists with obesity.[13, 14] The inverse association between body mass index (BMI) and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) has been suggested irrespective of age, sex, latitude, population group, cut-offs to define vitamin D deficiency,[13, 15, 16] which may be related to a bidirectional relationship between adipose tissue and vitamin D metabolism, storage, and action.[17-22] Obesity has been shown to involve a chronic state of low-grade inflammation that dysregulates glucose, lipid, and energy metabolism, termed metaflammation.[23-25] In addition to metabolic dysregulation in the major peripheral organs that control energy flux,[26] metaflammation disturbs brain function, especially affecting brain areas that regulate energy and metabolic homeostasis, such as hypothalamus.[27-31] It has been suggested that vitamin D could play a role in anti-obesity which at least partly mediated by vitamin D receptor (VDR) in the adipocytes/ peripheral organs[32-35] and the brain.[35-37] Thus, this has given rise to the hypothesis that vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Assessment of vitamin D supplementation for obese and overweight subjects has

been obtaining growing attention in recent randomized clinical trials (RCTs). Several earlier reviews and meta-analyses of RCTs have examined the effect of Vitamin D supplementation on weight loss, some inflammatory or glycemic markers in overweight and obese individuals, with limited and less conclusive results.[32, 38-42] However, energy and metabolic homeostasis related biomarkers have not been clearly and fully investigated in the above studies. Therefore, we seek to undertake a comprehensive systematic review of RCTs to evaluate the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

METHODS

Study registration

This protocol has been registered on Prospero (registration number: CRD42021228981), and was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[43]

Inclusion criteria for study selection

Studies will be included for review if they met the following inclusion criteria:

Participants: adult participants defined as being overweight or obese [BMI≥25 kg/m2 (overweight), BMI≥ 30 kg/m2 (obese)].[44] No restrictions will be assigned with regards to gender, race, geographical distribution and diseases of the participants enrolled in the study.

Intervention: participants in the experimental group should be treated with Vitamin D supplementation. Any vitamin D or its analogue supplementation will be qualified. There will be no limitations of routes of administration (oral or intramuscular), dose

and duration.

Comparison: no vitamin D supplementation under the same treatment program, placebo or sham control.

Outcome: primary outcomes: energy metabolism outcomes such as total energy expenditure (TEE), resting metabolic rate (RMR), resting energy expenditure (REE), basal and maximal oxygen consumption rate, bioenergetic health index (BHI); glucose and lipid metabolism outcomes such as fasting plasma concentration of glucose and insulin, homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for β cell function (HOMA-β), glycated hemoglobin (HbA1c), lipid (cholesterol and triglycerides) profiles, plasma levels of adipokines (adiponectin, leptin). secondary outcomes: anthropometric and body composition parameters such as height, weight, waist to hip ratio (WHR), BMI, fat mass (FM), fat-free mass (FFM), serum 25-hydroxyvitamin D [25(OH)D] concentration, adverse events, etc.

Study design and language: we will include only RCTs published in the English language.

Studies will be excluded if they were quasi-randomized trials and other types of studies, reported in books, conference proceedings or dissertations, or did not have available data for analysis.

Search methods for identification of studies

We will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to the date of the searches. A search

will be conducted using a combination of medical subject heading (MeSH) terms, free-text words and Boolean operators. The concepts of "participants" and "intervention" will be combined with the "AND" operator. Participants are defined as overweight and obese subjects, and intervention is defined as Vitamin D supplementation. For each concept, we will combine synonyms and Medical Subject Headings terms with the "OR" operator. A manual search of the reference lists of all relevant research articles will be performed to identify additional studies.

Data collection

Study selection

The bibliographic software Endnote (version X7) will be used to store, organize, and manage all the references. After removing duplicate articles, titles, abstracts and keywords of articles retrieved will be screened independently by two authors (NYS and YH) with predefined criteria to identify eligible studies. After preliminary screening, we will review the full text of potentially eligible articles in detail, to further assess eligibility, and reasons for exclusion will be recorded. Any disagreement between the two review authors will be resolved by discussion or with consultation of a third author.

Data extraction and management

Two authors (NYS and YH) will independently extract relevant data from the selected studies using a predefined data acquisition form. The extracted data will include the following items:

1. General information: first author, title, journal, publication year, country, study setting, ethical approval, trial registration and funding source.

2. Trial characteristics: study design, method of randomization, allocation concealment, incomplete outcome data, blinding (participants, researchers and outcome assessors).
3. Intervention: intervention (type, form, dose, and duration of vitamin D supplement provided); comparison intervention (form, dose, and duration of placebo provided).
4. Participants: participant demographics, baseline characteristics, inclusion/exclusion criteria, total number and number in each group, assessment of compliance and withdrawals.
5. Outcomes: primary and other outcomes, adverse events, duration of follow-up, intention-to-treat (ITT) analysis.

Possible discrepancies will be resolved through discussion or with consultation of a third author. if necessary, we may also contact the original authors for additional relevant information.

Assessment of risk of bias in included studies

This review will use the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions as methodological criteria.[45] The risk of bias for selected trials will be independently assessed by two authors (NYS and YH) based on the following criteria: random sequence generation; allocation concealment; blinding of participants, researchers and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. Trials will be rated as low risk, unclear risk or high risk or in each domain after evaluation. Possible disagreement will be resolved through discussion or with consultation of a third author.

Data analysis and synthesis

The Cochrane Review Manager software (version 5.3) will be used for meta-analysis. In our study, meta-analysis concerning effects of vitamin D supplement will be conducted if two or more studies used the same outcome measure or measured similar constructs.

The summary results will be computed in different way by data type. The continuous data will be analyzed using standardized mean differences (SMD) with 95% confidence interval (CI), while the odds ratio (OR) with 95% CI will be computed to analyze the dichotomous data.

Heterogeneity across the studies will be analyzed by the chi-squared test and I^2 statistic.[45, 46] If P>0.1, I^2<50%, fixed effects model will be used; If P>0.1, $I^2 \geqq 50\%$, random effects model will be used, substantial heterogeneity is considered in this case; If P $\leq$0.1, statistically significant is considered, subgroup analysis or a narrative description will be carried out.[45]

If applicable, prespecified subgroups will be conducted to explore factors that might impact the strength of the effect, such as type of vitamin D supplement; form of vitamin D supplement; whether there exists comorbid condition or not; age group. [45]

When possible, we will perform sensitivity analyses on the following factors to explore the influence of study quality on outcomes, such as allocation concealment, blinding of outcomes assessors, drop outs, ITT analysis, small research.[45]

If more than ten trials are included in a result of a meta-analysis, a funnel plot will be constructed to assess the potential publication bias. [45]

The quality of the evidence will be evaluated by GRADEpro software (version 3) at 4 levels (high, moderate, low, or very low) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[47] Two authors (NYS and YH) will evaluate the quality of evidence using GRADE, and possible discrepancy will be resolved through discussion or with consultation of a third author.

Patient and public involvement

Not applicable. This systematic review protocol does not directly involve patients and the general public. Data will be collected from published articles retrieved from main databases and manual search.

Ethics and dissemination

Ethical approval will not be required for the performance of this review protocol. Results of this research will be disseminated in a peer-review journal.

DISCUSSION

This protocol was registered prospectively in PROSPERO and developed in accordance with the PRISMA-P. This review will systematically and comprehensively assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. This review protocol provides an overview of the current situation in this area, and we hope that this study would be helpful to provide a valuable reference for future evidence-based as well as fundamental research to refine vitamin D supplementation in clinical practice and public health.

Contributors NYS, YH and ARZ contributed to the conception and design of the study. NYS registered the protocol in the PROSPERO database. All authors participated in the data acquisition, analysis and interpretation. NYS and YH performed the statistical analysis. YH drafted the manuscript. NYS and ARZ revised the manuscript critically for important intellectual content. All authors approved the final manuscript. NYS is the guarantor of the review.

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Competing interests We declare that there is no conflict of interest regarding the publication of this paper.

Patient consent for publication Not required.

Ethical approval Ethical approval will not be required for the performance of this protocol for a systematic review.

Data sharing No additional data are available.

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

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Main Document Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Main Document Page 3
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Main Document Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Main Document Page 10
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 NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review Main Document Page 11
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Main Document Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Main Document Page 5-6
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Main Document Page 5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Main Document Page 6-7
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 Main Document Page 6-7
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Main Document Page 7-8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Main Document Page 7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Main Document Page 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Main Document Page 7-8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Main Document Page 7-8
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 Main Document Page 8
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Main Document Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Main Document Page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Main Document Page
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Main Document Page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Main Document Page 9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Main Document Page 10

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Key words: vitamin D; obesity and overweight; energy homeostasis; metabolic homeostasis; systematic review; protocol

ABSTRACT

Introduction Obesity and vitamin D deficiency are both major public health problems. According to the pathophysiological mechanism of obesity as well as the bidirectional relationship between obesity and vitamin D metabolism and storage, vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Objectives Our review will assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

Methods and analysis In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), we will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to the date of the searches. A manual search of the reference lists of all relevant research articles will be performed to identify additional studies. We will include randomized controlled trials published in English examining effects of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. Two reviewers will independently complete the article selection, data extraction and rating. The bias tool from the Cochrane Handbook for

Systematic Reviews of Interventions will be used to assess the methodological quality of the included studies. Narrative or quantitative synthesis will be done depending on the available data.

Ethics and dissemination Ethical approval will not be required for this review. The results of this review will be disseminated in a peer-review journal.

Registration details PROSPERO International prospective register of systematic reviews registration number: CRD42021228981.

Strengths and limitations of this study

- The study will be conducted in accordance with the PRISMA and recommendations of the Cochrane handbook, which are well-recognized approaches for conducting and reporting of systematic reviews.
- Two reviewers will independently complete the article selection, data extraction and rating and possible disagreement will be resolved by discussion or with consultation of a third author.
- Different protocols of Vitamin D supplementation may lead to a large degree of heterogeneity.
- If applicable, prespecified subgroups will be conducted to exclude differences related to vitamin D supplement protocol, comorbid condition or age group.
- When possible, sensitivity analyses will be conducted to test whether the conclusions are robust.

INTRODUCTION

The definition of overweight and obesity is abnormal or excessive fat accumulation that may impair health.[1] With the continued increasing of prevalence across the world, overweight and obesity has been described as a global pandemic.[2-5] Since 1975, the prevalence of obesity worldwide has nearly tripled.[1] In 2016, over a third of adults worldwide were overweight and 13% were obese;[1, 6] over 340 million children and adolescents aged above 5 were overweight or obese.[1, 6] If this trend continues, it has been projected that up to 57.8% of the world's adult population could be either overweight or obese by 2030.[7] The high prevalence of overweight and obesity, combined with the associated disease burden as well as higher all-cause mortality, makes it a global public health challenge.[8, 9] Moreover, the disease burden of overweight and obesity has been greatly magnified by the current COVID-19 pandemic, as overweight and obesity were represented an unfavorable factor for COVID-19 severity and mortality.[10-12]

Vitamin D deficiency is another important public health issue, which often coexists with obesity.[13, 14] The inverse association between body mass index (BMI) and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) has been suggested irrespective of age, sex, latitude, population group, cut-offs to define vitamin D deficiency,[13, 15, 16] which may be related to a bidirectional relationship between adipose tissue and vitamin D metabolism, storage, and action.[17-23] Obesity has been shown to involve a chronic state of low-grade inflammation that dysregulates glucose, lipid, and energy metabolism, termed metaflammation.[24-26] In addition to metabolic

dysregulation in the major peripheral organs that control energy flux,[27] metaflammation disturbs brain function, especially affecting brain areas that regulate energy and metabolic homeostasis, such as hypothalamus.[28-32] It has been suggested that vitamin D could play a role in anti-obesity which at least partly mediated by vitamin D receptor (VDR) in the adipocytes/peripheral organs[33-36] and the brain.[36-38]Thus, this has given rise to the hypothesis that vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Assessment of vitamin D supplementation for obese and overweight subjects has been obtaining growing attention in recent randomized clinical trials (RCTs). Several earlier reviews and meta-analyses of RCTs have examined the effect of Vitamin D supplementation on weight loss, serum vitamin D concentration, some inflammatory or glycemic markers in overweight and obese individuals with or without comorbid condition, with limited and less conclusive results.[13, 33, 39-45] However, energy and metabolic homeostasis related biomarkers have not been clearly and fully investigated in the above studies. Therefore, we seek to undertake a comprehensive systematic review of RCTs to evaluate the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

METHODS

Study registration

This protocol has been registered on Prospero (registration number: CRD42021228981), and was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[46] The final study will

be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement,[47] under the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.[48]

Inclusion criteria for study selection

Studies will be included for review if they met the following inclusion criteria:

Participants: adult participants defined as being overweight or obese [BMI≥25 kg/m2 (overweight), BMI≥ 30 kg/m2 (obese)].[49] No restrictions will be assigned with regards to gender, race, geographical distribution and diseases of the participants enrolled in the study.

Intervention: participants in the experimental group should be treated with Vitamin D supplementation. Any vitamin D or its analogue supplementation will be qualified. There will be no limitations of routes of administration (oral or intramuscular), dose and duration.

Comparison: no vitamin D supplementation under the same treatment program, placebo or sham control.

Outcome measures: primary outcomes: energy metabolism outcomes such as total energy expenditure (TEE), resting metabolic rate (RMR), resting energy expenditure (REE), basal and maximal oxygen consumption rate, bioenergetic health index (BHI); glucose and lipid metabolism outcomes such as fasting plasma concentration of glucose and insulin, homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for β cell function (HOMA-β), glycated hemoglobin (HbA1c), lipid (cholesterol and triglycerides) profiles, plasma levels of adipokines

(adiponectin, leptin). secondary outcomes: anthropometric and body composition parameters such as height, weight, waist to hip ratio (WHR), BMI, fat mass (FM), fat-free mass (FFM), serum 25-hydroxyvitamin D [25(OH)D] concentration, adverse events, etc.

Study design and language: we will include only RCTs published in the English language.

Studies will be excluded if they were quasi-randomized trials and other types of studies, reported in books, conference proceedings or dissertations, or did not have available data for analysis.

Search methods for identification of studies

We will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to the date of the searches. A search will be conducted using a combination of medical subject heading (MeSH) terms, free-text words and Boolean operators. The concepts of "participants", "intervention" and "RCTs" will be combined with the "AND" operator. Participants are defined as overweight and obese subjects, and intervention is defined as Vitamin D supplementation. For each concept, we will combine synonyms and Medical Subject Headings terms with the "OR" operator. We will develop the search strategy for MEDLINE (via Ovid) (see supplementary material Appendix 1. Search Strategy Example) and adapt this strategy for the other databases. A manual search of the reference lists of all relevant research articles will be performed to identify additional

studies.

Data collection

Study selection

The bibliographic software Endnote (version X7) will be used to store, organize, and manage all the references. After removing duplicate articles, titles, abstracts and keywords of articles retrieved will be screened independently by two authors (NYS and YH) with predefined criteria to identify eligible studies. After preliminary screening, we will review the full text of potentially eligible articles in detail, to further assess eligibility, and reasons for exclusion will be recorded. Any disagreement between the two review authors will be resolved by discussion or with consultation of a third author. The final selection procedure will follow the PRISMA guidelines,[47] and is presented in Figure 1.

Data extraction and management

Two authors (NYS and YH) will independently extract relevant data from the selected studies using a predefined data acquisition form. The extracted data will include the following items:

1. General information: first author, title, journal, publication year, country, study setting, ethical approval, trial registration and funding source.
2. Trial characteristics: study design, method of randomization, allocation concealment, incomplete outcome data, blinding (participants, researchers and outcome assessors).
3. Intervention: intervention (type, form, dose, and duration of vitamin D supplement

provided); comparison intervention (form, dose, and duration of placebo provided).

4. Participants: participant demographics, baseline characteristics, inclusion/exclusion criteria, total number and number in each group, assessment of compliance and withdrawals.
5. Outcomes: primary and other outcomes, adverse events, duration of follow-up, intention-to-treat (ITT) analysis.

Possible discrepancies will be resolved through discussion or with consultation of a third author. if necessary, we may also contact the original authors for additional relevant information.

Assessment of risk of bias in included studies

This review will use the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions as methodological criteria.[48] The risk of bias for selected trials will be independently assessed by two authors (NYS and YH) based on the following criteria: random sequence generation; allocation concealment; blinding of participants, researchers and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. Trials will be rated as low risk, unclear risk or high risk or in each domain after evaluation. Possible disagreement will be resolved through discussion or with consultation of a third author.

Data analysis and synthesis

The Cochrane Review Manager software (version 5.3) will be used for meta-analysis. In our study, meta-analysis concerning effects of vitamin D supplement will be conducted if two or more studies used the same outcome measure or measured similar

constructs.

The summary results will be computed in different way by data type. The continuous data will be analyzed using standardized mean differences (SMD) with 95% confidence interval (CI), while the odds ratio (OR) with 95% CI will be computed to analyze the dichotomous data.

Heterogeneity across the studies will be analyzed by the chi-squared test and I^2 statistic.[48, 50] If P>0.1, I^2<50%, fixed effects model will be used; If P>0.1, $I^2 \geqq 50\%$, random effects model will be used, substantial heterogeneity is considered in this case; If P $\leq$0.1, statistically significant is considered, subgroup analysis or a narrative description will be carried out. [48]

If applicable, prespecified subgroups will be conducted to explore factors that might impact the strength of the effect, such as type of vitamin D supplement; form of vitamin D supplement; whether there exists comorbid condition or not; age group. [48]

When possible, we will perform sensitivity analyses on the following factors to explore the influence of study quality on outcomes, such as allocation concealment, blinding of outcomes assessors, drop outs, ITT analysis, small research. [48]

If more than ten trials are included in a result of a meta-analysis, a funnel plot will be constructed to assess the potential publication bias. [48]

The quality of the evidence will be evaluated by GRADEpro software (version 3) at 4 levels (high, moderate, low, or very low) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[51] Two authors (NYS and YH) will evaluate the quality of evidence using GRADE, and

possible discrepancy will be resolved through discussion or with consultation of a third author.

Patient and public involvement

This systematic review protocol does not directly involve patients and the general public. Data will be collected from published articles retrieved from main databases and manual search.

Ethics and dissemination

Ethical approval will not be required for the performance of this review protocol. Results of this research will be disseminated in a peer-review journal.

DISCUSSION

This protocol was registered prospectively in PROSPERO and developed in accordance with the PRISMA-P. This review will systematically and comprehensively assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. This review protocol provides an overview of the current situation in this area, and we hope that this study would be helpful to provide a valuable reference for future evidence-based as well as fundamental research to refine vitamin D supplementation in clinical practice and public health.

Contributors NYS, YH and ARZ contributed to the conception and design of the study. NYS registered the protocol in the PROSPERO database. YH drafted the protocol. NYS and ARZ revised the protocol critically for important intellectual content. ML and XY designed the search strategy. NYS, YH, ARZ, ML and XY participated in the design of data acquisition, analysis and

interpretation. All authors have read and approved the final protocol. NYS is the guarantor of the protocol and the final review.

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Competing interests We declare that there is no conflict of interest regarding the publication of this paper.

Patient consent for publication Not required.

Ethical approval Ethical approval will not be required for the performance of this protocol for a systematic review.

Data sharing No additional data are available.

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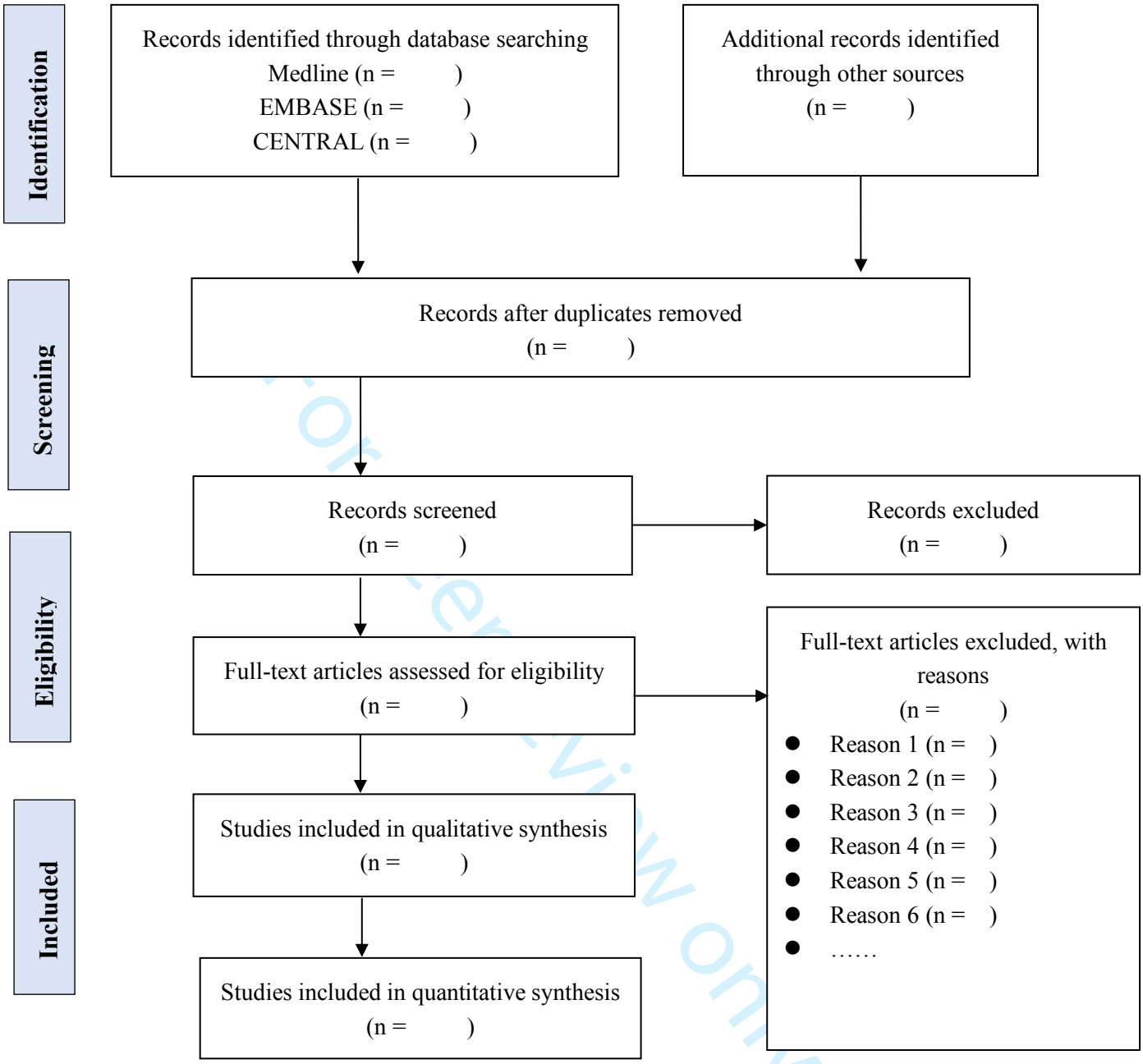
FIGURE LEGENDS

Figure 1. Flowchart of the study selection procedure



Appendix 1

Search Strategy Example: MEDLINE (via Ovid) search

Terms specific to vitamin D

#1 exp Vitamin D/

#2 (Vitamin D OR Vitamin D2 OR Vitamin D3 OR Cholecalciferol* OR Calciol OR Hydroxycholecalciferol* OR Hydroxyvitamin* D OR Calcitriol OR Calcidiol OR Calderol OR Calcifediol OR Hydroxycholecalciferol OR Dedrogyl OR Hidroferol OR Ergocalciferol* OR Calciferol* OR Ercalcidiol OR Hydroxycalciferol OR Dihydrotachysterol OR Tachystin OR Dihydrotachysterin OR Calcamine OR Alphacalcidol OR alfacalcidol). ab,ti.

#3 #1 OR #2

Terms specific to overweight and obesity

#4 exp overweight/

#5 exp obesity/

#6 exp adiposity/

#7 (overweight* OR over weight* OR obes* OR adipos* OR fat). ab,ti.

#8 #4 OR #5 OR #6 OR #7

Terms for identifying randomized controlled trials

#9 exp randomized controlled trial/

#10 randomized controlled trial.pt.

#11 controlled clinical trial.pt.

#12 (random* OR placebo OR sham OR trial OR groups). ab,ti.

#13 #9 OR #10 OR #11 OR #12

Combination of terms to identify randomized controlled trials of vitamin D for obese and overweight subjects

#3 AND #8 AND #13

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

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Main Document Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Main Document Page 3
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Main Document Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Main Document Page 11-12
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 NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review Main Document Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Main Document Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Main Document Page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Main Document Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Main Document Page 6-7
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 Main Document Page 7, Appendix 1. Search Strategy Example
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Main Document Page 8-10

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Main Document Page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Main Document Page 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Main Document Page 6-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Main Document Page 6-7
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 Main Document Page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Main Document Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Main Document Page 10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Main Document Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Main Document Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Main Document Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Main Document Page 10-11

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

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BMJ Open

Vitamin D supplementation and energy and metabolic homeostasis in obese and overweight subjects: a protocol for a systematic review

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Manuscript ID	bmjopen-2021-051230.R2
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Date Submitted by the Author:	30-Aug-2021
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Complementary medicine, Global health, Evidence based practice
Keywords:	NUTRITION & DIETETICS, PUBLIC HEALTH, DIABETES & ENDOCRINOLOGY

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Vitamin D supplementation and energy and metabolic homeostasis in obese and overweight subjects: a protocol for a systematic review

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Key words: vitamin D; obesity and overweight; energy homeostasis; metabolic homeostasis; systematic review; protocol

ABSTRACT

Introduction Obesity and vitamin D deficiency are both major public health problems. According to the pathophysiological mechanism of obesity as well as the bidirectional relationship between obesity and vitamin D metabolism and storage, vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Objectives Our review will assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

Methods and analysis In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), we will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to June 2021. A manual search of the reference lists of all relevant research articles will be performed to identify additional studies. We will include randomized controlled trials (RCTs) published in English examining effects of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. RCTs with multiple vitamin D groups will also be included. Two reviewers will independently complete the article selection, data extraction and rating. The bias tool from the Cochrane Handbook for Systematic Reviews of Interventions

will be used to assess the methodological quality of the included studies. Narrative or quantitative synthesis will be done depending on the available data. The planned start and end dates for the study is 1 February 2021 and 1 March 2022.

Ethics and dissemination Ethical approval will not be required for this review. The results of this review will be disseminated in a peer-review journal.

Registration details PROSPERO International prospective register of systematic reviews registration number: CRD42021228981.

Strengths and limitations of this study

- The study will be conducted in accordance with the PRISMA and recommendations of the Cochrane handbook, which are well-recognized approaches for conducting and reporting of systematic reviews.
- Two reviewers will independently complete the article selection, data extraction and rating and possible disagreement will be resolved by discussion or with consultation of a third author.
- Different protocols of Vitamin D supplementation may lead to a large degree of heterogeneity.
- If applicable, prespecified subgroup analyses will be conducted to exclude differences related to vitamin D supplement protocol, comorbid condition or age group.
- When possible, sensitivity analyses will be conducted to test whether the conclusions are robust.

INTRODUCTION

The definition of overweight and obesity is abnormal or excessive fat accumulation that may impair health.[1] With the continued increasing of prevalence across the world, overweight and obesity has been described as a global pandemic.[2-5] Since 1975, the prevalence of obesity worldwide has nearly tripled.[1] In 2016, over a third of adults worldwide were overweight and 13% were obese;[1, 6] over 340 million children and adolescents aged above 5 were overweight or obese.[1, 6] If this trend continues, it has been projected that up to 57.8% of the world's adult population could be either overweight or obese by 2030.[7] The high prevalence of overweight and obesity, combined with the associated disease burden as well as higher all-cause mortality, makes it a global public health challenge.[8, 9] Moreover, the disease burden of overweight and obesity has been greatly magnified by the current COVID-19 pandemic, as overweight and obesity were represented an unfavorable factor for COVID-19 severity and mortality.[10-12]

Vitamin D deficiency is another important public health issue, which often coexists with obesity.[13, 14] The inverse association between body mass index (BMI) and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) has been suggested irrespective of age, sex, latitude, population group, cut-offs to define vitamin D deficiency,[13, 15, 16] which may be related to a bidirectional relationship between adipose tissue and vitamin D metabolism, storage, and action.[17-23] Obesity has been shown to involve a chronic state of low-grade inflammation that dysregulates glucose,

lipid, and energy metabolism, termed metaflammation.[24-26] In addition to metabolic dysregulation in the major peripheral organs that control energy flux,[27] metaflammation disturbs brain function, especially affecting brain areas that regulate energy and metabolic homeostasis, such as hypothalamus.[28-32] It has been suggested that vitamin D could play a role in anti-obesity which at least partly mediated by vitamin D receptor (VDR) in the adipocytes/peripheral organs[33-36] and the brain.[36-38]Thus, this has given rise to the hypothesis that vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

Assessment of vitamin D supplementation for obese and overweight subjects has been obtaining growing attention in recent randomized clinical trials (RCTs). Several earlier reviews and meta-analyses of RCTs have examined the effect of Vitamin D supplementation on weight loss, serum vitamin D concentration, some inflammatory or glycemic markers in overweight and obese individuals with or without comorbid condition, with limited and less conclusive results.[13, 33, 39-45] However, energy and metabolic homeostasis related biomarkers have not been clearly and fully investigated in the above studies. Therefore, we seek to undertake a comprehensive systematic review of RCTs to evaluate the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

METHODS

Study registration

This protocol has been registered on Prospero (registration number: CRD42021228981), and was developed according to the Preferred Reporting Items for

Systematic Review and Meta-Analysis Protocols (PRISMA-P).[46] The final study will be developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement,[47] under the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.[48]

Inclusion criteria for study selection

Studies will be included for review if they met the following inclusion criteria:

Participants: adult participants defined as being overweight or obese [BMI≥25 kg/m2 (overweight), BMI≥ 30 kg/m2 (obese)].[49] No restrictions will be assigned with regards to gender, race, geographical distribution and diseases of the participants enrolled in the study.

Intervention: participants in the experimental group should be treated with Vitamin D supplementation. Any vitamin D or its analogue supplementation will be qualified. There will be no limitations of routes of administration (oral or intramuscular), dose and duration.

Comparison: no vitamin D supplementation under the same treatment program, placebo or sham control.

Outcome measures: primary outcomes: energy metabolism outcomes such as total energy expenditure (TEE), resting metabolic rate (RMR), resting energy expenditure (REE), basal and maximal oxygen consumption rate, bioenergetic health index (BHI); glucose and lipid metabolism outcomes such as fasting plasma concentration of glucose and insulin, homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for β cell function (HOMA-β), glycated hemoglobin

(HbA1c), lipid (cholesterol and triglycerides) profiles, plasma levels of adipokines (adiponectin, leptin). secondary outcomes: anthropometric and body composition parameters such as height, weight, waist to hip ratio (WHR), BMI, fat mass (FM), fat-free mass (FFM), serum 25-hydroxyvitamin D [25(OH)D] concentration, adverse events, etc.

Study design and language: we will include only RCTs published in the English language.

Studies will be excluded if they were quasi-randomized trials and other types of studies, reported in books, conference proceedings or dissertations, or did not have available data for analysis.

Search methods for identification of studies

We will retrieve relevant literatures across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to June 2021. A search will be conducted using a combination of medical subject heading (MeSH) terms, free-text words and Boolean operators. The concepts of "participants", "intervention" and "RCTs" will be combined with the "AND" operator. Participants are defined as overweight and obese subjects, and intervention is defined as Vitamin D supplementation. For each concept, we will combine synonyms and Medical Subject Headings terms with the "OR" operator. We will develop the search strategy for MEDLINE (via Ovid) (see supplementary material Appendix 1. Search Strategy Example) and adapt this strategy for the other databases. A manual search of the

reference lists of all relevant research articles will be performed to identify additional studies.

Data collection

Study selection

The bibliographic software Endnote (version X7) will be used to store, organize, and manage all the references. After removing duplicate articles, titles, abstracts and keywords of articles retrieved will be screened independently by two authors (NYS and YH) with predefined criteria to identify eligible studies. After preliminary screening, we will review the full text of potentially eligible articles in detail, to further assess eligibility, and reasons for exclusion will be recorded. Any disagreement between the two review authors will be resolved by discussion or with consultation of a third author. The final selection procedure will follow the PRISMA guidelines,[47] and is presented in Figure 1.

Data extraction and management

Two authors (NYS and YH) will independently extract relevant data from the selected studies using a predefined data acquisition form. The extracted data will include the following items:

1. General information: first author, title, journal, publication year, country, study setting, ethical approval, trial registration and funding source.
2. Trial characteristics: study design, method of randomization, allocation concealment, incomplete outcome data, blinding (participants, researchers and outcome assessors).

3. Intervention: intervention (type, form, dose, and duration of vitamin D supplement provided); comparison intervention (form, dose, and duration of placebo provided).
4. Participants: participant demographics, baseline characteristics, inclusion/exclusion criteria, total number and number in each group, assessment of compliance and withdrawals.
5. Outcomes and related information: primary and other outcomes, adverse events, duration of follow-up, intention-to-treat (ITT) analysis.

   Possible discrepancies will be resolved through discussion or with consultation of a third author. if necessary, we may also contact the original authors for additional relevant information.

Assessment of risk of bias in included studies

This review will use the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions as methodological criteria.[48] The risk of bias for selected trials will be independently assessed by two authors (NYS and YH) based on the following criteria: random sequence generation; allocation concealment; blinding of participants, researchers and outcome assessors; incomplete outcome data; selective reporting; and other sources of bias. Trials will be rated as low risk, unclear risk or high risk or in each domain after evaluation. Possible disagreement will be resolved through discussion or with consultation of a third author.

Data analysis and synthesis

The Cochrane Review Manager software (version 5.3) will be used for meta-analysis. In our study, meta-analysis concerning effects of vitamin D supplement will be

conducted if two or more studies used the same outcome measure or measured similar constructs.

The summary results will be computed in different way by data type. The continuous data will be analyzed using standardized mean differences (SMD) with 95% confidence interval (CI), while the odds ratio (OR) with 95% CI will be computed to analyze the dichotomous data.

Heterogeneity across the studies will be analyzed by the chi-squared test and I^2 statistic.[48, 50] If P>0.1, I^2<50%, fixed effects model will be used; If P>0.1, $I^2 \geqq 50\%$, random effects model will be used, substantial heterogeneity is considered in this case; If P $\leq$0.1, statistically significant is considered, subgroup analysis or a narrative description will be carried out. [48]

If applicable, prespecified subgroups will be conducted to explore factors that might impact the strength of the effect, such as type of vitamin D supplement; form of vitamin D supplement; whether there exists comorbid condition or not; age group. [48]

When possible, we will perform sensitivity analyses on the following factors to explore the influence of study quality on outcomes, such as allocation concealment, blinding of outcomes assessors, drop outs, ITT analysis, small research. [48]

If more than ten trials are included in a result of a meta-analysis, a funnel plot will be constructed to assess the potential publication bias. [48]

The quality of the evidence will be evaluated by GRADEpro software (version 3) at 4 levels (high, moderate, low, or very low) according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[51] Two

authors (NYS and YH) will evaluate the quality of evidence using GRADE, and possible discrepancy will be resolved through discussion or with consultation of a third author.

Patient and public involvement

This systematic review protocol does not directly involve patients and the general public. Data will be collected from published articles retrieved from main databases and manual search.

Ethics and dissemination

Ethical approval will not be required for the performance of this review protocol. Results of this research will be disseminated in a peer-review journal.

DISCUSSION

This protocol was registered prospectively in PROSPERO and developed in accordance with the PRISMA-P. This review will systematically and comprehensively assess the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. This review protocol provides an overview of the current situation in this area, and we hope that this study would be helpful to provide a valuable reference for future evidence-based as well as fundamental research to refine vitamin D supplementation in clinical practice and public health.

Contributors NYS, YH and ARZ contributed to the conception and design of the study. NYS registered the protocol in the PROSPERO database. YH drafted the protocol. NYS and ARZ revised the protocol critically for important intellectual content. ML and XY designed the search strategy.

NYS, YH, ARZ, ML and XY participated in the design of data acquisition, analysis and interpretation. All authors have read and approved the final protocol. NYS is the guarantor of the protocol and the final review.

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Competing interests We declare that there is no conflict of interest regarding the publication of this paper.

Patient consent for publication Not required.

Ethical approval Ethical approval will not be required for the performance of this protocol for a systematic review.

Data sharing No additional data are available.

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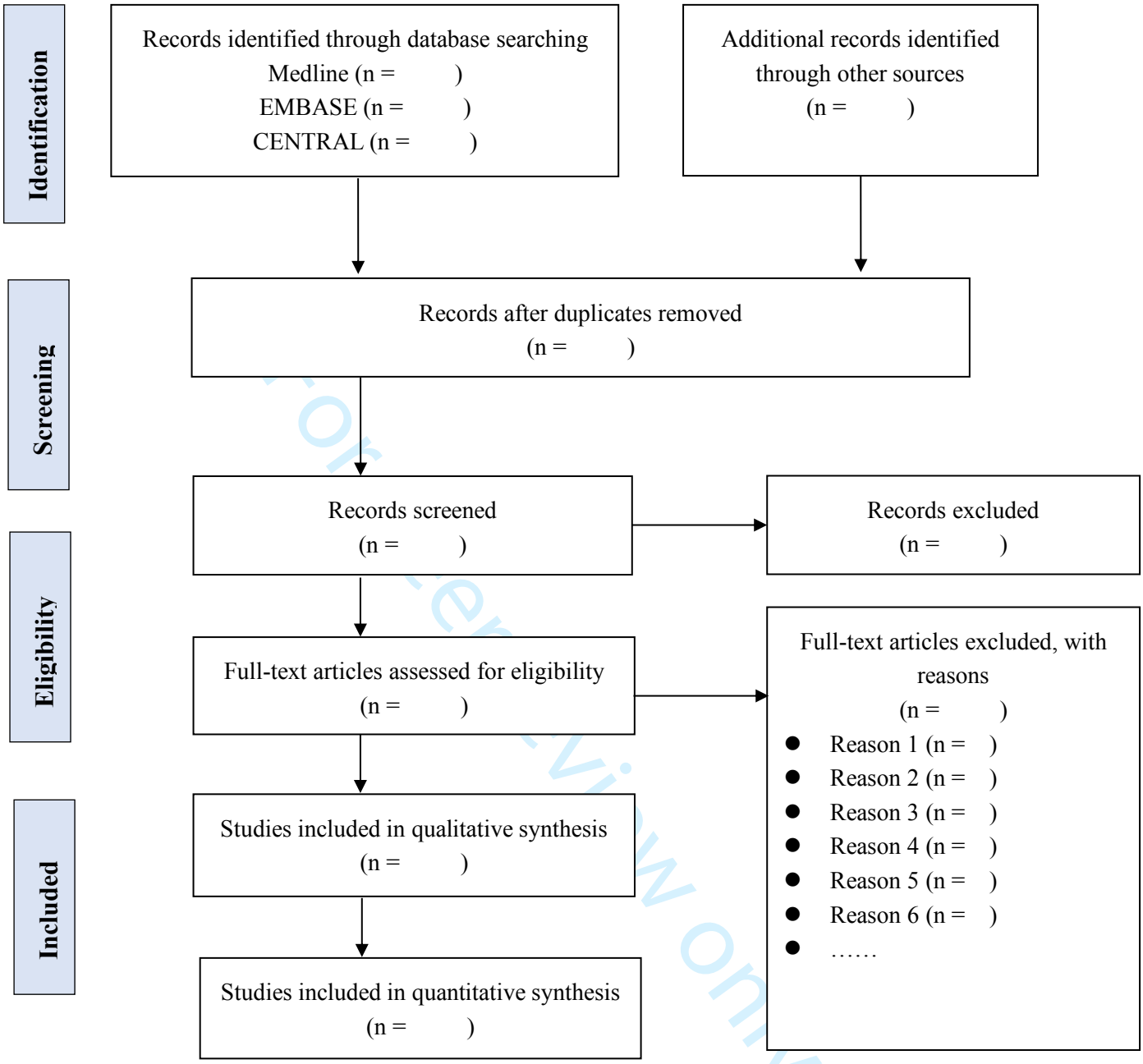
FIGURE LEGENDS

Figure 1. Flowchart of the study selection procedure



Appendix 1

Search Strategy Example: MEDLINE (via Ovid) search

Terms specific to vitamin D

#1 exp Vitamin D/

#2 (Vitamin D OR Vitamin D2 OR Vitamin D3 OR Cholecalciferol* OR Calciol OR Hydroxycholecalciferol* OR Hydroxyvitamin* D OR Calcitriol OR Calcidiol OR Calderol OR Calcifediol OR Hydroxycholecalciferol OR Dedrogyl OR Hidroferol OR Ergocalciferol* OR Calciferol* OR Ercalcidiol OR Hydroxycalciferol OR Dihydrotachysterol OR Tachystin OR Dihydrotachysterin OR Calcamine OR Alphacalcidol OR alfacalcidol). ab,ti.

#3 #1 OR #2

Terms specific to overweight and obesity

#4 exp overweight/

#5 exp obesity/

#6 exp adiposity/

#7 (overweight* OR over weight* OR obes* OR adipos* OR fat). ab,ti.

#8 #4 OR #5 OR #6 OR #7

Terms for identifying randomized controlled trials

#9 exp randomized controlled trial/

#10 randomized controlled trial.pt.

#11 controlled clinical trial.pt.

#12 (random* OR placebo OR sham OR trial OR groups). ab,ti.

#13 #9 OR #10 OR #11 OR #12

Combination of terms to identify randomized controlled trials of vitamin D for obese and overweight subjects

#3 AND #8 AND #13

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

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Main Document Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Main Document Page 3
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Main Document Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Main Document Page 11-12
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 NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review Main Document Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Main Document Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Main Document Page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Main Document Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Main Document Page 6-7
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 Main Document Page 7, Appendix 1. Search Strategy Example
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Main Document Page 8-10

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Main Document Page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Main Document Page 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Main Document Page 6-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Main Document Page 6-7
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 Main Document Page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Main Document Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Main Document Page 10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Main Document Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Main Document Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Main Document Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Main Document Page 10-11

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

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Vitamin D supplementation and energy and metabolic homeostasis in obese and overweight subjects: a protocol for a systematic review

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Key words: vitamin D; obesity and overweight; energy homeostasis; metabolic homeostasis; systematic review; protocol

ABSTRACT

Introduction Obesity and vitamin D deficiency are major public health problems. According to the pathophysiological mechanism of obesity as well as the bidirectional relationship between obesity and vitamin D metabolism and storage, vitamin D supplementation in obese and overweight subjects could have beneficial effects on the energy and metabolic homeostasis. This review will assess the efficacy of vitamin D supplementation on the energy and metabolic homeostasis in overweight and obese subjects.

Methods and analysis: In accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), we retrieved the relevant literature from the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL), from inception to June 2021. A manual search of the reference lists of all the relevant research articles will be performed to identify additional studies. We will include randomised controlled trials (RCTs) published in English that examine the effects of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. RCTs with multiple vitamin D groups will also be included. Two reviewers will independently complete the article selection, data extraction, and rating. The bias tool from the Cochrane Handbook for Systematic

Reviews of Interventions was used to assess the methodological quality of the included studies. A narrative or quantitative synthesis will be performed based on the available data. The planned start and end dates for the study were 1 February 2021 and 1 March 2022.

Ethics and dissemination Ethical approval will not be required for this review. The results of this review will be disseminated in a peer-reviewed journal.

Registration details PROSPERO International prospective register of systematic review registration number: CRD42021228981.

Strengths and limitations of this study

- The study will be conducted in accordance with the PRISMA and recommendations of the Cochrane handbook, which are well-recognized approaches for conducting and reporting of systematic reviews.
- Two reviewers will independently complete the article selection, data extraction, and rating, and possible disagreements will be resolved by discussion or consultation with a third author.
- Different protocols for vitamin D supplementation may lead to a large degree of heterogeneity.
- If applicable, pre-specified subgroup analyses will be conducted to exclude the differences related to the vitamin D supplementation protocol, comorbid condition, or age group.
- When possible, sensitivity analyses will be conducted to test whether the

conclusions are robust.

INTRODUCTION

The definition of overweight and obesity is abnormal or excessive fat accumulation that may impair health.[1] With the continued increase in the prevalence worldwide, overweight and obesity have been described as a global pandemic.[2-5] Since 1975, the worldwide prevalence of obesity has nearly tripled.[1] In 2016, over a third of adults worldwide were overweight and 13% were obese;[1, 6] over 340 million children and adolescents aged above 5 years were overweight or obese.[1, 6] If this trend continues, it has been projected that up to 57.8% of the world's adult population could be either overweight or obese by 2030.[7] The high prevalence of overweight and obesity, combined with the associated disease burden as well as higher all-cause mortality makes it a global public health challenge.[8, 9] Moreover, the disease burden of overweight and obesity has been greatly magnified by the current COVID-19 pandemic, as overweight and obesity were represented as an unfavourable factor for COVID-19 severity and mortality.[10-12]

Vitamin D deficiency is another important public health issue, which often coexists with obesity.[13, 14] The inverse association between the body mass index (BMI) and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) has been suggested irrespective of age, sex, latitude, population group, or cut-offs to define vitamin D deficiency,[13, 15, 16] which may be related to a bidirectional relationship between the adipose tissue and vitamin D metabolism, storage, and action.[17-23] Obesity

has been shown to involve a chronic state of low-grade inflammation that dysregulates glucose, lipid, and energy metabolism, termed metaflammation.[24-26] In addition to the metabolic dysregulation in the major peripheral organs that control the energy flux,[27] metaflammation disturbs the brain function, especially affecting the brain areas that regulate energy and metabolic homeostasis, such as the hypothalamus.[28-32] It has been suggested that vitamin D could play a role in anti-obesity, which at least was partly mediated by the vitamin D receptor (VDR) in the adipocytes/peripheral organs[33-36] and the brain.[36-38] Thus, this has given rise to the hypothesis that vitamin D supplementation in obese and overweight subjects could have beneficial effects on their energy and metabolic homeostasis.

The assessment of vitamin D supplementation in obese and overweight subjects has been gaining increasing attention in recent randomised clinical trials (RCTs). Several earlier reviews and meta-analyses of RCTs have examined the effect of vitamin D supplementation on weight loss, serum vitamin D concentration, and inflammatory or glycaemic markers in overweight and obese individuals with or without comorbid conditions, with limited and less conclusive results.[13, 33, 39-45] However, the energy and metabolic homeostasis-related biomarkers have not been clearly and fully investigated in the above studies. Therefore, we sought to undertake a comprehensive systematic review of RCTs to evaluate the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects.

METHODS

Study registration

This protocol has been registered on Prospero (registration number: CRD42021228981) and was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[46] The final study was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement,[47] under the guidance of the Cochrane Handbook for Systematic Reviews of Interventions.[48]

Inclusion criteria for study selection

Studies will be included for review if they meet the following inclusion criteria:

Participants: The adult participants were defined as being overweight or obese (BMI ≥25 kg/m^2 [overweight], BMI≥ 30 kg/m^2 [obese)].[49] No restrictions will be assigned with regard to the sex, race, geographical distribution, and diseases of the participants enrolled in the study.

Intervention: Participants in the experimental group were treated with vitamin D supplementation. Any vitamin D and its analogue supplementation will be qualified. There will be no limitations on the routes of administration (oral or intramuscular), dose, and duration.

Comparison: No vitamin D supplementation under the same treatment program, placebo, or sham control.

Outcome measures: Primary outcomes: The energy metabolism outcomes, such as the total energy expenditure (TEE), resting metabolic rate (RMR), resting energy expenditure (REE), basal and maximal oxygen consumption rate, bioenergetic health index (BHI), glucose and lipid metabolism outcomes, such as the fasting plasma

concentration of glucose and insulin, homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for β-cell function (HOMA-β), glycated haemoglobin (HbA1c), lipid (cholesterol and triglycerides) profiles, and plasma levels of adipokines (adiponectin and leptin). The secondary outcomes included anthropometric and body composition parameters, such as height, weight, waist to hip ratio (WHR), BMI, fat mass (FM), fat-free mass (FFM), serum 25-hydroxyvitamin D [25(OH)D] concentration, and adverse events.

Study design and language: We will include only RCTs published in English.

Studies will be excluded if they were quasi-randomized trials and other types of studies, reported in books, conference proceedings, dissertations, or did not have available data for analysis.

Search methods for the identification of studies

We will retrieve relevant literature across the following electronic bibliographic databases: MEDLINE/PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL), from inception to June 2021. A search will be conducted using a combination of medical subject heading (MeSH) terms, free-text words, and Boolean operators. The concepts of "participants", "intervention", and "RCTs" will be combined with the "AND" operator. The participants will be defined as overweight and obese subjects, and the intervention is defined as vitamin D supplementation. For each concept, we will combine synonyms and Medical Subject Headings terms with the "OR" operator. We will be developing a search strategy for MEDLINE via Ovid (see Supplementary Material Appendix 1. Search Strategy

Example) and adapt this strategy for the other databases. A manual search of the reference lists of all the relevant research articles will be performed to identify additional studies.

Data collection

Study selection

The bibliographic software Endnote (version X7) will be used to store, organise, and manage all the references. After the removal of duplicate articles, the titles, abstracts, and keywords of the retrieved articles will be screened independently by two authors (NYS and YH) with predefined criteria to identify the eligible studies. After preliminary screening, we will review the full text of potentially eligible articles in detail, to further assess the eligibility, and the reasons for exclusion will be recorded. Any disagreement between the two review authors will be resolved by discussion or consultation with a third author. The final selection procedure will be following the PRISMA guidelines,[47] and is presented in Figure 1.

Data extraction and management

Two authors (NYS and YH) will independently extract the relevant data from the selected studies using a predefined data acquisition form. The extracted data will include the following items:

1. General information: The first author, title, journal, publication year, country, study setting, ethical approval, trial registration, and the funding source.
2. Trial characteristics: study design, method of randomisation, allocation concealment, incomplete outcome data, and blinding (participants, researchers, and

outcome assessors).

3. Intervention: intervention (type, form, dose, and duration of vitamin D supplement provided) and comparison intervention (form, dose, and duration of placebo provided).
4. Participants: Participant demographics, baseline characteristics, inclusion/exclusion criteria, total number, and number in each group, and the assessment of compliance and withdrawals.
5. Outcomes and related information: primary and other outcomes, adverse events, duration of follow-up, and intention-to-treat (ITT) analysis.

Possible discrepancies will be resolved through discussion or consultation with a third author. If necessary, we may also contact the original authors for additional relevant information.

Assessment of risk of bias in included studies

This review will use the bias tool from the Cochrane Handbook for Systematic Reviews of Interventions as the methodological criteria.[48] The risk of bias for the selected trials will be independently assessed by two authors (NYS and YH) based on the following criteria: random sequence generation, allocation concealment, blinding of participants, researchers and outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. The trials will be rated as low risk, unclear risk, or high risk, or in each domain after evaluation. Possible disagreements will be resolved through discussion or consultation with a third author.

Data analysis and synthesis

The Cochrane Review Manager software (version 5.3) will be used for the meta-analysis. In our study, a meta-analysis concerning the effects of vitamin D supplementation will be conducted if two or more studies used the same outcome measure or measured similar constructs.

The summary results are computed in different ways by the data type. Continuous data will be analysed using standardised mean differences (SMD) with 95% confidence interval (CI), while the odds ratio (OR) with 95% CI will be computed to analyse the dichotomous data.

Heterogeneity across the studies will be analysed using the chi-squared test and I^2 statistic.[48, 50] If $P>0.1$, $I^2<50\%$, a fixed effects model will be used; if $P>0.1$, $I^2\geq50\%$, a random effects model will be used, substantial heterogeneity is considered in this case; if $P\leq0.1$, statistical significance is considered, and a subgroup analysis or a narrative description will be carried out. [48]

If applicable, pre-specified subgroups will be conducted to explore factors that might impact the strength of the effect, such as the type of vitamin D supplement; form of vitamin D supplement; whether a comorbid condition exists or not; and the age group. [48]

When possible, we will perform sensitivity analyses on the following factors to explore the influence of the study quality on the outcomes, such as allocation concealment, blinding of the outcome assessors, dropout, and ITT analysis. [48]

If more than ten trials are included in a result of a meta-analysis, a funnel plot will be constructed to assess the potential publication bias. [48]

The quality of the evidence will be evaluated using GRADEpro software (version 3) at four levels (high, moderate, low, or very low) according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[51] Two authors (NYS and YH) will evaluate the quality of the evidence using GRADE, and possible discrepancies will be resolved through discussion or consultation with a third author.

Patient and public involvement

This systematic review protocol does not directly involve patients or the general public. The data will be collected from published articles retrieved from the main databases and manual searches.

Ethics and dissemination

Ethical approval will not be required for the performance of this review protocol. The results of this research will be disseminated in a peer-reviewed journal.

DISCUSSION

This protocol was registered prospectively in PROSPERO and developed in accordance with the PRISMA-P. This review systematically and comprehensively assessed the efficacy of vitamin D supplementation on energy and metabolic homeostasis in overweight and obese subjects. This review protocol provides an overview of the current situation in this area, and we hope that this study will be helpful in providing a valuable reference for future evidence-based and fundamental research to refine vitamin D supplementation in clinical practice and public health.

Contributors NYS, YH, and ARZ contributed to the conception and design of the study. NYS registered the protocol in the PROSPERO database. YH drafted the protocol. NYS and ARZ revised the protocol critically for important intellectual content. ML and XY designed the search strategy. NYS, YH, ARZ, ML and XY participated in the design of data acquisition, analysis and interpretation. All authors have read and approved the final protocol. NYS is the guarantor of the protocol and the final review.

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Competing interests: We declare that there is no conflict of interest regarding the publication of this paper.

Patient consent for publication Not required.

Ethical approval: Ethical approval will not be required for the performance of this protocol for a systematic review.

Data sharing No additional data are available.

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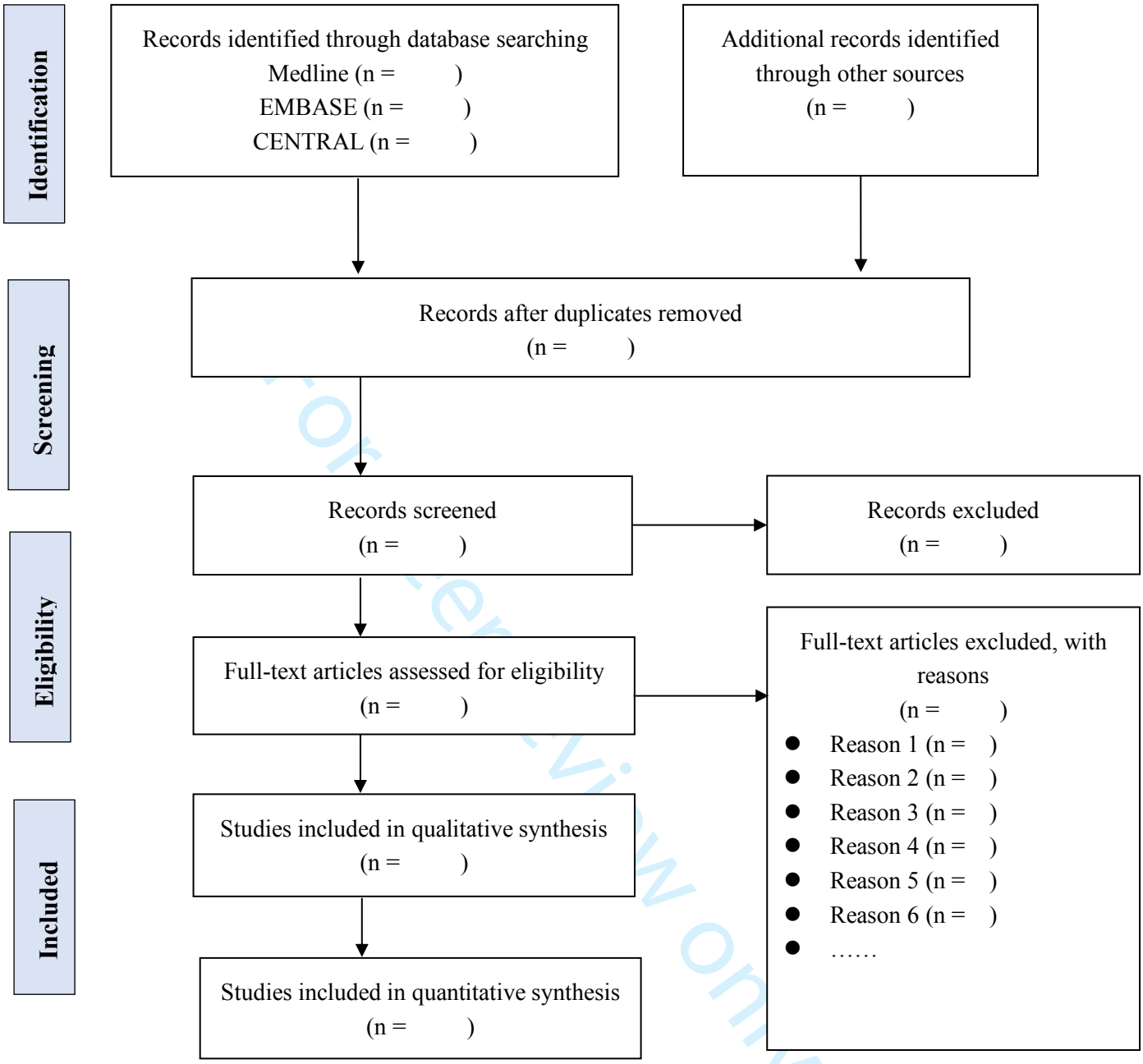
evidence and strength of recommendations. *BMJ* 2008; 336(7650):924-6.

FIGURE LEGENDS

Figure 1. Flowchart of the study selection procedure



Appendix 1

Search Strategy Example: MEDLINE (via Ovid) search

Terms specific to vitamin D

#1 exp Vitamin D/

#2 (Vitamin D OR Vitamin D2 OR Vitamin D3 OR Cholecalciferol* OR Calciol OR Hydroxycholecalciferol* OR Hydroxyvitamin* D OR Calcitriol OR Calcidiol OR Calderol OR Calcifediol OR Hydroxycholecalciferol OR Dedrogyl OR Hidroferol OR Ergocalciferol* OR Calciferol* OR Ercalcidiol OR Hydroxycalciferol OR Dihydrotachysterol OR Tachystin OR Dihydrotachysterin OR Calcamine OR Alphacalcidol OR alfacalcidol). ab,ti.

#3 #1 OR #2

Terms specific to overweight and obesity

#4 exp overweight/

#5 exp obesity/

#6 exp adiposity/

#7 (overweight* OR over weight* OR obes* OR adipos* OR fat). ab,ti.

#8 #4 OR #5 OR #6 OR #7

Terms for identifying randomized controlled trials

#9 exp randomized controlled trial/

#10 randomized controlled trial.pt.

#11 controlled clinical trial.pt.

#12 (random* OR placebo OR sham OR trial OR groups). ab,ti.

#13 #9 OR #10 OR #11 OR #12

Combination of terms to identify randomized controlled trials of vitamin D for obese and overweight subjects

#3 AND #8 AND #13

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

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review Main Document Page 1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number Main Document Page 3
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author Main Document Page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review Main Document Page 11-12
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 NA
Support:		
Sources	5a	Indicate sources of financial or other support for the review Main Document Page 12
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known Main Document Page 4-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Main Document Page 6-7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review Main Document Page 6-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage Main Document Page 6-7
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 Main Document Page 7, Appendix 1. Search Strategy Example
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review Main Document Page 8-10

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) Main Document Page 8-9
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators Main Document Page 8-9
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications Main Document Page 6-10
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Main Document Page 6-7
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 Main Document Page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised Main Document Page 9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ) Main Document Page 10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) Main Document Page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned Main Document Page 10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) Main Document Page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) Main Document Page 10-11

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

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