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Selenium and bone health: a protocol for a systematic review and meta-analysis

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Title: Selenium and bone health: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Bone health affects the ability of human body to stay active and the degradation of bone health can cause considerable morbidity and mortality. The factors related to bone health play an important role in preventing osteoporosis and its adverse consequences. However, the aetiology of osteoporosis has not been fully elucidated. The deficiency of the trace element selenium may be one of the risk factors for the development of osteoporosis. Previous studies have investigated the effects of selenium on osteoporosis; however, the results are inconclusive. Therefore, the present study aimed to systematically examine the existing literature on the associations between dietary or serum selenium and bone mineral density (BMD), osteoporosis, or osteoporotic fractures, and to quantify such associations through meta-analysis.

Methods and analysis PubMed, Embase and Cochrane Library will be searched by applying the specified search strategy to identify relevant studies up to October 2019. The outcomes will include BMD and the prevalence or incidence of osteoporosis and osteoporotic fractures. For the dietary or serum selenium and BMD, osteoporosis, or osteoporotic fractures pooled analyses, estimates will be expressed as the mean difference, and the pooled odds ratio, relative risk, hazard ratio or beta coefficient and corresponding 95% confidence intervals. The heterogeneity of the studies and the publication bias will be investigated accordingly. To assess the quality and the risk of bias of the included studies, the Newcastle-Ottawa Scale or the Cochrane risk of bias assessment tool will be used where appropriate.

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Ethics and dissemination Since no private and confidential patient data will be

contained in the reporting, approval from an ethics committee is not required. The

results will be published in a peer-reviewed journal. The study raises no ethical issues.

PROSPERO registration number CRD42019147188

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Strengths and limitations of the study

▸ As the first meta-analysis that evaluated the associations between dietary

selenium intake or serum selenium concentrations and BMD, osteoporosis, or

osteoporotic fractures, the findings of this study will deepen the existing

knowledge base on the pathogenesis of osteoporosis, and promote the

development of effective preventive or treatment strategies.

▸ Two investigators will perform the study selection, data extraction and quality

assessments independently, and disagreements will be resolved by discussions.

▸ Both the quality and the risk of bias will be properly assessed for the included

studies by applying the Newcastle-Ottawa Quality Scale or the Cochrane risk of

bias assessment tool where appropriate.

▸ The differences in study design and sample characteristics may lead to a high

level of heterogeneity.

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INTRODUCTION

Bone health affects the ability of human body to stay active throughout life, and the

degradation of bone health can cause considerable morbidity and mortality.[1][2] The

various factors related to bone health at different ages play an important role in

preventing osteoporosis and its adverse consequences.[3] Osteoporosis, which is

characterized by low bone mass and microarchitectural deterioration of bone tissue, is

a systemic skeletal disease that can result in increased bone fragility and increased

fracture risk as a consequence.[3][4] With an ageing population, the socioeconomic and

medical impact of osteoporosis will increase rapidly. It is estimated that by 2020,

there will be over 200 million people worldwide affected by osteoporosis, and the

expenses related to osteoporosis will rise to about $25.3 billion by 2025.[5]

Osteoporosis is practically diagnosed by the presence of a fragility fracture or low

bone mineral density (BMD) which is a commonly used proxy measure what accounts

for approximately 70% of bone strength.[3] However, osteoporosis can occur without a

known underlying cause, and its aetiology has not been fully elucidated.

Nutrition has a significant influence on bone health and nutritional support is

among the crucial cornerstones of the prevention of osteoporosis.[6] The trace element

selenium, as a critical constituent of about 25 selenoenzymes, plays an essential role

in a variety of physiological processes and it has been confirmed that the beneficial

effects of selenium are related to human health.[7][8] Some studies collectively suggested

that the preservation of selenoproteins in bone was essential to normal skeletal

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development.[9] Animal studies have shown that selenium-deprivation can retard

growth and change bone metabolism.[10] Such effects are associated with reduced

BMD, impaired bone microarchitecture and increased bone resorption. Previous

clinical studies have investigated the effects of selenium on bone health, however, the

results are inconclusive. Some suggested that serum and dietary selenium were

positively correlated with BMD,[11 12] while other showed that neither serum nor

dietary selenium was associated with osteoporosis.[13 14] Meanwhile, some case-control

studies revealed that the dietary intake of selenium was associated with reduced risk

of osteoporotic hip fracture.[15 16]

Meta-analysis is an effective tool for revealing trends that may not be apparent,

and it also helps in establishing clinical policies and guidelines. Thus, we aimed to

systematically examine the existing literature on the associations between dietary or

serum selenium concentrations and BMD, osteoporosis, or osteoporotic fractures, and

to quantify such associations through meta-analysis where feasible.

METHODS

Study design

The aim of this meta-analysis is to investigate the associations between dietary intake

or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures. This

protocol was developed according to the Preferred Reporting Items for Systematic

Review and Meta-Analyses Protocols (PRISMA-P) 2015 Statement,[17] and has been

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registered in the international prospective register of systematic reviews PROSPERO

network (registration number: CRD42019147188).

Eligibility criteria

Types of studies

The meta-analysis will include both interventional and observational studies, inclusive

of case-control studies, randomized controlled trials, cross-sectional studies and

cohort studies which focus on the associations between dietary intake or serum levels

of selenium and BMD, osteoporosis, or osteoporotic fractures.

Types of participants

The participants in the included studies must be with information on dietary intake or

serum levels of selenium, and with data of BMD or diagnosis of osteoporosis or

osteoporotic fractures. No sex, ethnicity, economic status, geographical limitations, or

education restrictions will be applied.

Types of exposure/intervention

Two main forms of exposure will be included, i.e., dietary intake selenium and serum

levels of selenium.

Types of outcome measures

Primary outcomes will include BMD values and the prevalence or incidence of

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osteoporosis. The secondary outcome will be the prevalence or incidence of

osteoporotic fractures. There will be no restriction on site and measuring method.

Information sources

Systematic literature searches will be undertaken across PubMed, Embase and

Cochrane Library by applying the specified search strategy to identify relevant studies

up to October 2019 on each platform or database. In addition, the references of the

retrieved literature will be manually searched, and the relevant studies and systematic

reviews will be scanned for additional eligible studies.

Search strategy

Keyword terms or medical subject heading terms (MESH) will be used to search for

eligible studies in the databases mentioned above. The electronic search strategy is

presented in **Table 1**. All the search terms will be adapted for different syntax rules of

the databases.

Study selection

The search results from the three electronic databases will be sent to Endnote. After

removing duplicates, two investigators will be responsible for screening the titles and

abstracts of all the retrieved literature to identify eligible studies. In case that the

eligibility of a study cannot be determined, the full text will be reviewed for inclusion

according to prespecified inclusion and exclusion criteria. There will be no restriction

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on the publication date and language. The study selection process will be summarized

based on the PRISMA flow diagram. Disagreements between the two investigators

will be resolved by discussing with a third investigator.

Data extraction

Two investigators will be engaged to independently extract the following data in a

standardized collection form: publication information (author, year of publishing);

study information (country of origin, study setting, data sources, study period);

demographic information (sample size, age, and sex distribution); exposure

information (dietary or serum selenium concentrations); outcome information (BMD,

osteoporosis, osteoporotic fractures). Then, the effect sizes (mean difference [MD],

odds ratio [OR], relative risk [RR], hazard ratio [HR] or beta coefficient [β]) will be

either extracted directly or calculated based on the information in the original studies

whenever possible. If the relevant data is not reported in an included study, the

missing information will be obtained by contacting the authors directly as far as

possible. The two investigators responsible for reviewing the literature will resolve

any disagreements through discussions, and a third independent investigator may be

involved into the discussion if required.

Assessment of risk of bias

The Cochrane risk of bias assessment tool will be used to assess the quality of

RCTs,[18] while the Newcastle-Ottawa Quality Scale (NOS) will be used to assess the

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quality of observational studies.[19] Two investigators will be engaged to conduct the

risk of bias assessment independently, and disagreements will be resolved through

discussions.

Data analysis

Firstly, the characteristics of included studies will be summarized using baseline

tables and narrative texts. The proposed study will calculate the MD, the pooled OR,

RR, HR or β and the corresponding 95% CIs. Then, Cochrane's Q test and the I^2

statistics will be used to assess the heterogeneity of the included studies, where p

value > 0.05 of the Q statistics and I^2 value $< 50\%$ indicate statistical homogeneity. If

the included studies are found to be statistically homogeneous, the fixed effects

models will be used to pool the data during meta-analysis; otherwise, the random

effects models will be used instead. Statistical analyses will be conducted in Review

Manager-5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane

Collaboration, 2014) and Stata-11.0 (StataCorp LP, College Station, TX) statistical

software. Statistical significance is considered at p value < 0.05.

Assessment of publication bias

If the number of included studies is greater than 10, a funnel plot will be constructed

and the Egger test will be conducted to observe the publication bias. The existence of

publication bias is confirmed when the funnel plot shows an asymmetric pattern.

Then, the bias, if any, will be explained through discussions after assessment.

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Patient and public involvement

As our systematic review will be implemented based on published studies, no patients

and members of the public will be directly involved. All the data to be used in this

study already exists in the published literature and/or the aforementioned sources.

Ethics and dissemination

As this meta-analysis will be performed based on published studies, and no private

and confidential patient data will be contained in the reporting, approval from an

ethics committee is not required. The results will be disseminated through publication

in a peer- reviewed journal. The study raises no ethical issues.

DISCUSSION

To our best knowledge, there are at least 10 studies that have investigated the

associations between dietary or serum selenium concentrations and BMD,

osteoporosis, or osteoporotic fractures. Of them, two studies suggested that serum and

dietary selenium were likely to positively correlate with BMD,[11][12] and three studies

showed that dietary selenium was negatively associated with osteoporotic fractures.[15]

[16][20] On the contrary, one study found no association between dietary selenium and

BMD,[21] and four studies reported that neither serum nor dietary selenium was related

to osteoporosis.[13][14][22][23]

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The health of the skeletal system is important for elderly people.[1] Nowadays,

osteoporosis is becoming increasingly more prevalent with population aging around

the world, presenting a severe public health problem in the future.[5] Selenium is an

essential element for bones, and plays an important role in skeletal development.[10] An

in-depth understanding of the relationship between selenium and bone health is useful

for designing early life interventions. The sample size of previous studies might have

not always been big enough to achieve sufficient statistical power, which could

explain, at least in part, why the statistical difference in some instances was not

reached, despite the obvious trends. Therefore, the aim of this systematic review and

meta-analysis is to summarize the available evidence to investigate the associations

between selenium and bone health. The results of this study will deepen the existing

knowledge base on the pathogenesis of osteoporosis, and promote the development of

preventive or treatment strategies in this field.

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COMPETING INTERESTS

The authors declare that they have no conflict of interest.

PATIENT CONSENT FOR PUBLICATION

Not required.

AUTHOR'S CONTRIBUTIONS

Conceptualization: Yilun Wang and Dongxing Xie

Data curation: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

Methodology: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

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Writing – original draft: Ning Wang and Dongxing Xie

Writing – review & editing: Yilun Wang and Tuo Yang

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Table 1 Electronic search strategy in Pubmed

Number	Search terms
1	selenium[mesh] or "selenious acid"[mesh] or selen*[tiab] or selepen[tiab] or organoselen*[tiab] or natriumselen*[tiab] or methylseleninic[tiab] or methylselenium[tiab] or selenomethionin*[tiab] or selenit*[tiab]
2	bone demineralization[mesh] or bone density[mesh] or osteopenia[mesh] or osteoporosis[mesh] or bone densitometry[mesh] or osteoporo*[tiab] or bone densit*[tiab] or bone loss[tiab] or osteomalacia[tiab] or osteodystrophy[tiab] or bone deminerali?ation[tiab] or osteopenia[tiab] or bone mass[tiab] or bone mineral content*[tiab] or bone defect*[tiab] or bone strength[tiab] or BMC[tiab] or "fracture"[mesh] or fracture* [tiab]
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	P1
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 (such as PROSPERO) and registration number | P4, P7-8 |

Authors

| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | P1-2 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | P14-15 |

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	P14
Sponsor	#5b	Provide name for the review funder and / or sponsor	P14
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	P14

Introduction

| Rationale | #6 | Describe the rationale for the review in the context of what is | P6-7 |

already known

Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P8-9

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	P8-9
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	P9
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	P18
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P10-11
Study records - 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)	P9-10
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	P10

	process		processes for obtaining and confirming data from investigators	
4	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	P10
11	Outcomes and prioritization	[#13](#)	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P8
19	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	P10-11
29	Data synthesis	[#15a](#)	Describe criteria under which study data will be quantitatively synthesised	P10-11
34	Data synthesis	[#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 I2, Kendall's τ)	P11
44	Data synthesis	[#15c](#)	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
49	Data synthesis	[#15d](#)	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
55	Meta-bias(es)	[#16](#)	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	P11

studies)

| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | n/a |

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1 **Title: Selenium and bone health: a protocol for a systematic review and meta-**

2 **analysis**

3

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14

15 **Abbreviated title:** Selenium and bone health

16

17 **Keywords:** selenium, osteoporosis, serum, dietary, meta-analysis

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20

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1   **ABSTRACT**

2   **Introduction** Bone health affects the ability of human body to stay active and the

3   degradation of bone health can cause considerable morbidity and mortality. The

4   factors related to bone health play an important role in preventing osteoporosis and its

5   adverse consequences. However, the risk factors of osteoporosis has not been fully

6   elucidated. The deficiency of the trace element selenium may be one of the risk

7   factors for the development of osteoporosis. Previous studies have investigated the

8   effects of selenium on osteoporosis; however, the results are inconclusive. Therefore,

9   the present study aimed to systematically examine the existing literature on the

10   associations between dietary or serum selenium and bone mineral density (BMD),

11   osteoporosis, or osteoporotic fractures, and to quantify such associations through

12   meta-analysis.

13   **Methods and analysis** PubMed, Embase and Cochrane Library will be searched by

14   applying the specified search strategy to identify relevant studies up to October 2019.

15   Both interventional and observational studies in humans will be included. The

16   outcomes will include BMD and the prevalence or incidence of osteoporosis and

17   osteoporotic fractures. For the dietary or serum selenium and BMD, osteoporosis, or

18   osteoporotic fractures pooled analyses, estimates will be expressed as the mean

19   difference, and the pooled odds ratio, relative risk, hazard ratio or beta coefficient and

20   corresponding 95% confidence intervals. The heterogeneity of the studies and the

21   publication bias will be investigated accordingly. To assess the quality and the risk of

22   bias of the included studies, the Newcastle-Ottawa Scale or the Cochrane risk of bias

3

1 assessment tool will be used where appropriate.

2 **Ethics and dissemination** Since no private and confidential patient data will be

3 contained in the reporting, approval from an ethics committee is not required. The

4 results will be published in a peer-reviewed journal. The study raises no ethical issues.

5 **PROSPERO registration number** CRD42019147188

4

1   **Strengths and limitations of the study**

2   ▸ As the first meta-analysis that evaluated the associations between dietary

3   selenium intake or serum selenium concentrations and BMD, osteoporosis, or

4   osteoporotic fractures, the findings of this study will deepen the existing

5   knowledge base on the pathogenesis of osteoporosis, and promote the

6   development of effective preventive or treatment strategies.

7   ▸ Two investigators will perform the study selection, data extraction and quality

8   assessments independently, and disagreements will be resolved by discussions.

9   ▸ Both the quality and the risk of bias will be properly assessed for the included

10   studies by applying the Newcastle-Ottawa Quality Scale or the Cochrane risk of

11   bias assessment tool where appropriate.

12   ▸ The differences in study design and sample characteristics may lead to a high

13   level of heterogeneity.

14   ▸ Both prospective and retrospective studies will be included in this meta-analysis,

15   which may also incur bias and impact the final results .

16

5

1 **INTRODUCTION**

2 Bone health affects the ability of the human body to stay active throughout life, and

3 the degradation of bone health can cause considerable morbidity and mortality.[1][2] The

4 various factors related to bone health at different ages play an important role in

5 preventing osteoporosis and its adverse consequences.[3] Bone health is mainly

6 reflected in diseases caused by bone mass loss, such as osteoporosis and fragility

7 fracture.[4][5] Osteoporosis, which is characterized by low bone mass and

8 microarchitectural deterioration of bone tissue, is a systemic skeletal disease that can

9 result in increased bone fragility and increased fracture risk as a consequence.[3][6] With

10 an ageing population, the socioeconomic and medical impact of osteoporosis will

11 increase rapidly. It is estimated that by 2020, there will be over 200 million people

12 worldwide affected by osteoporosis, and the expenses related to osteoporosis will rise

13 to about $25.3 billion by 2025.[7] Osteoporosis is practically diagnosed by the presence

14 of a fragility fracture or low bone mineral density (BMD) which is a commonly used

15 proxy measure that accounts for approximately 70% of bone strength.[3] However,

16 osteoporosis can occur without a known underlying cause, and its risk factors have

17 not been fully elucidated.

18

19 Nutrition has a significant influence on bone health and adequate nutrition is

20 among the crucial cornerstones of the prevention of osteoporosis.[8] The trace element

21 selenium, as a critical constituent of about 25 selenoenzymes, plays an essential role

22 in a variety of physiological processes and it has been confirmed that the beneficial

6

1   effects of selenium are related to human health.[9][10] Some studies collectively

2   suggested that the preservation of selenoproteins in bone was essential to normal

3   skeletal development.[11] Animal studies have shown that selenium-deprivation can

4   retard growth and change bone metabolism.[12] Such effects are associated with

5   reduced BMD, impaired bone microarchitecture and increased bone resorption.

6   Previous clinical studies have investigated the effects of selenium on bone health,

7   however, the results are inconclusive. Some suggested that serum and dietary

8   selenium were positively correlated with BMD,[13][14] while other showed that neither

9   serum nor dietary selenium was associated with osteoporosis.[15][16] Meanwhile, some

10 case-control studies revealed that the dietary intake of selenium was associated with

11 reduced risk of osteoporotic hip fracture.[17][18]

12

13   Meta-analysis is an effective tool for revealing trends that may not be apparent,

14 and it also helps in establishing clinical policies and guidelines. Thus, we aimed to

15 systematically examine the existing literature on the associations between dietary or

16 serum selenium concentrations and BMD, osteoporosis, or osteoporotic fractures, and

17 to quantify such associations through meta-analysis where feasible.

18

19 **METHODS**

20 **Study design**

21 The aim of this meta-analysis is to investigate the associations between dietary intake

22 or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures. This

7

1 protocol was developed according to the Preferred Reporting Items for Systematic

2 Review and Meta-Analyses Protocols (PRISMA-P) 2015 Statement,[19] and has been

3 registered in the international prospective register of systematic reviews PROSPERO

4 network (registration number: CRD42019147188).

5

6 **Eligibility criteria**

7 Types of studies

8 The meta-analysis will include both interventional and observational studies in

9 humans, inclusive of case-control studies, randomized controlled trials, cross-

10 sectional studies and cohort studies which focus on the associations between dietary

11 intake or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures.

12

13 Types of participants

14 The participants in the included studies must have provided information on dietary

15 intake or serum levels of selenium, and BMD measures or diagnosis of osteoporosis

16 or osteoporotic fractures. No age, sex, ethnicity, economic status, geographical

17 limitations, or education restrictions will be applied.

18

19 Types of exposure/intervention

20 Two main forms of exposure will be included, i.e., dietary intake selenium and serum

21 levels of selenium.

22

8

1   Types of outcome measures

2   Primary outcomes will include T-score , BMD values and the prevalence or incidence

3   of osteoporosis. The diagnostic criteria of osteoporosis shall be based on the included

4   articles, such as the presence of a fragility fracture or using BMD criteria. The

5   secondary outcome will be the prevalence or incidence of osteoporotic fractures.

6   There will be no restriction on site and measuring method, but we will give priority to

7   extracting T-score for analysis rather than to extracting BMD values. When T-score is

8   not available, we will try to analyze BMD measured with Lunar and Hologic

9   machines separately.

10

11 **Information sources**

12 Systematic literature searches will be undertaken across PubMed, Embase and

13 Cochrane Library by applying the specified search strategy to identify relevant studies

14 up to October 2019 on each platform or database. In addition, the references of the

15 retrieved literature will be manually searched. And Grey literature will also be

16 searched included study registries (e.g., ClinicalTrials.gov and google scholar). The

17 relevant studies and systematic reviews will be scanned for additional eligible studies.

18

19 **Search strategy**

20 Keyword terms or medical subject heading terms (MESH) will be used to search for

21 eligible studies in the databases mentioned above. The electronic search strategy is

22 presented in **Table 1**. All the search terms will be adapted for different syntax rules of

9

1   the databases.

2

3   **Study selection**

4   The search results from the three electronic databases will be sent to Endnote. After

5   removing duplicates, two investigators will be responsible for screening the titles and

6   abstracts of all the retrieved literature to identify eligible studies. In case that the

7   eligibility of a study cannot be determined, the full text will be reviewed for inclusion

8   according to prespecified inclusion and exclusion criteria. There will be no restriction

9   on the publication date and language. The study selection process will be summarized

10   based on the PRISMA flow diagram. Disagreements between the two investigators

11   will be resolved by discussing with a third investigator.

12

13   **Data extraction**

14   Two investigators will be engaged to independently extract the following data in a

15   standardized collection form: publication information (author, year of publishing);

16   study information (country of origin, study setting, data sources, study period);

17   demographic information (sample size, age, and sex distribution); exposure

18   information (dietary or serum selenium concentrations); outcome information (T-

19   score , BMD values, the prevalence or incidence of osteoporosis or osteoporotic

20   fractures). Then, both the adjusted and unadjusted effect sizes (mean difference [MD],

21   odds ratio [OR], relative risk [RR], hazard ratio [HR] or beta coefficient [β]) will be

22   either extracted directly or calculated based on the information in the original studies

10

1   whenever possible. If the relevant data is not reported in an included study, the

2   missing information will be obtained by contacting the authors directly as far as

3   possible. The two investigators responsible for reviewing the literature will resolve

4   any disagreements through discussions, and a third independent investigator may be

5   involved into the discussion if required.

6

Assessment of risk of bias

8   The Cochrane risk of bias assessment tool will be used to assess the quality of

9   RCTs,[20] while the Newcastle-Ottawa Quality Scale (NOS) will be used to assess the

10   quality of observational studies.[21] Two investigators will be engaged to conduct the

11   risk of bias assessment independently, and disagreements will be resolved through

12   discussions.

13

Data analysis

15   Firstly, the characteristics of included studies will be summarized using baseline

16   tables and narrative texts. The proposed study will calculate the MD, the pooled OR,

17   RR, HR or β and the corresponding 95% CIs. Unadjusted risk estimates and adjusted

18   estimates will be pooled in the meta-analysis. Then, Cochrane's Q test and the I^2

19   statistics will be used to assess the heterogeneity of the included studies, where *p*

20   value > 0.05 of the Q statistics and I^2 value < 50% indicate statistical homogeneity.[22]

21   [23] If the included studies are found to be statistically homogeneous, the fixed effects

22   models will be used to pool the data during meta-analysis; otherwise, the random

11

1   effects models will be used instead. Statistical analyses will be conducted in Review

2   Manager-5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane

3   Collaboration, 2014) and Stata-11.0 (StataCorp LP, College Station, TX) statistical

4   software. Statistical significance is considered at p value < 0.05. Finally, to minimize

5   the heterogeneity between included studies, subgroup analyses based on different age,

6   sex, ethnicity, economic status, geographical limitations, or education restrictions will

7   be conducted where feasible.

8

Assessment of publication bias

10 If the number of included studies is greater than 10, a funnel plot will be constructed

11 and the Egger test will be conducted to observe the publication bias. The existence of

12 publication bias is confirmed when the funnel plot shows an asymmetric pattern.

13 Then, the bias, if any, will be explained through discussions after assessment.

14

Patient and public involvement

16 As our systematic review will be implemented based on published studies, no patients

17 and members of the public will be directly involved. All the data to be used in this

18 study already exists in the published literature and/or the aforementioned sources.

19

Ethics and dissemination

21 As this meta-analysis will be performed based on published studies, and no private

22 and confidential patient data will be contained in the reporting, approval from an

12

1 ethics committee is not required. The results will be disseminated through publication

2 in a peer- reviewed journal. The study raises no ethical issues.

3

4 **DISCUSSION**

5 The health of the skeletal system is important for elderly people.[1] An in-depth

6 understanding of the relationship between selenium and bone health is useful for

7 designing early life interventions. To our best knowledge, there are at least 10 studies

8 that have investigated the associations between dietary or serum selenium

9 concentrations and BMD, osteoporosis, or osteoporotic fractures. Of them, two

10 studies suggested that serum and dietary selenium were likely to positively correlate

11 with BMD,[13 14] and three studies showed that dietary selenium was negatively

12 associated with osteoporotic fractures.[17 18 24] On the contrary, one study found no

13 association between dietary selenium and BMD,[25] and four studies reported that

14 neither serum nor dietary selenium was related to osteoporosis.[15 16 26 27] Contradictory

15 results of these studies might be related to the differences in study design and sample

16 characteristics. So it's still controversial whether the contents of selenium can directly

17 influence BMD and affect the pathogenesis of osteoporosis. The sample size of

18 previous studies might have been too small to achieve sufficient statistical power,

19 which could explain, at least in part, why the statistical difference in some instances

20 was not reached, despite the obvious trends. Therefore, the aim of this systematic

21 review and meta-analysis is to summarize the available evidence to investigate the

22 associations between selenium and bone health. The results of this study will deepen

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1   2   3   4   5   6   7   8   9   10   11   12   13   14   15   16   17   18   19   20   21   22   23   24   25   26   27   28   29   30   31   32   33   34   35   36   37   38   39   40   41   42   43   44   45   46   47   48   49   50   51   52   53   54   55   56   57   58   59   60

1   the existing knowledge base on the pathogenesis of osteoporosis, and promote the

2   development of preventive or treatment strategies in this field.

14

1   **COMPETING INTERESTS**

2   The authors declare that they have no conflict of interest.

3

4   **PATIENT CONSENT FOR PUBLICATION**

5   Not required.

6

7   **FUNDING**

18

19 **AUTHOR'S CONTRIBUTIONS**

20 Conceptualization: Yilun Wang and Dongxing Xie

21 Data curation: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

22 Methodology: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

15

1 Writing – original draft: Ning Wang and Dongxing Xie

2 Writing – review & editing: Yilun Wang and Tuo Yang

16

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10   contents of elderly males in Beijing urban area. *Int J Clin Exp Med* 2015;8:19250-7.

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12   contents of postmenopausal women in Xi'an urban area. *Biol Trace Elem Res* 2009;131:205-14.

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1 **Table 1 Electronic search strategy in Pubmed**

Number	Search terms
1	selenium[mesh] or "selenious acid"[mesh] or selen*[tiab] or selepen[tiab] or organoselen*[tiab] or natriumselen*[tiab] or methylseleninic[tiab] or methylselenium[tiab] or selenomethionin*[tiab] or selenit*[tiab]
2	bone demineralization[mesh] or bone density[mesh] or osteopenia[mesh] or osteoporosis[mesh] or bone densitometry[mesh] or osteoporo*[tiab] or bone densit*[tiab] or bone loss[tiab] or osteomalacia[tiab] or osteodystrophy[tiab] or bone deminerali?ation[tiab] or osteopenia[tiab] or bone mass[tiab] or bone mineral content*[tiab] or bone defect*[tiab] or bone strength[tiab] or BMC[tiab] or "fracture"[mesh] or fracture* [tiab]
3	1 AND 2

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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

	Reporting Item	Page Number
Title		
Identification	#1a Identify the report as a protocol of a systematic review	P1
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 (such as PROSPERO) and registration number | P4, P7-8 |

Authors

| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | P1-2 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | P14-15 |

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	P14
Sponsor	#5b	Provide name for the review funder and / or sponsor	P14
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	P14

Introduction

| Rationale | #6 | Describe the rationale for the review in the context of what is | P6-7 |

already known

Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P8-9

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	P8-9
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	P9
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	P18
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P10-11
Study records - 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)	P9-10
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	P10

process		processes for obtaining and confirming data from investigators	
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	P10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P8
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	P10-11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	P10-11
Data synthesis	#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 I2, Kendall's τ)	P11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	P11

studies)

| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | n/a |

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Selenium and bone health: a protocol for a systematic review and meta-analysis

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1 **Title: Selenium and bone health: a protocol for a systematic review and meta-**

2 **analysis**

3

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16

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19 **Word count:** 1827

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1 **ABSTRACT**

2 **Introduction** Bone health affects the ability of human body to stay active and the

3 degradation of bone health can cause considerable morbidity and mortality. The

4 factors related to bone health play an important role in preventing osteoporosis and its

5 adverse consequences. However, the risk factors of osteoporosis has not been fully

6 elucidated. The deficiency of the trace element selenium may be one of the risk

7 factors for the development of osteoporosis. Previous studies have investigated the

8 effects of selenium on osteoporosis; however, the results are inconclusive. Therefore,

9 the present study aimed to systematically examine the existing literature on the

10 associations between dietary or serum selenium and bone mineral density (BMD),

11 osteoporosis, or osteoporotic fractures, and to quantify such associations through

12 meta-analysis.

13 **Methods and analysis** PubMed, Embase and Cochrane Library will be searched by

14 applying the specified search strategy to identify relevant studies up to October 2019.

15 Both interventional and observational studies in humans will be included. The

16 outcomes will include BMD and the prevalence or incidence of osteoporosis and

17 osteoporotic fractures. For the dietary or serum selenium and BMD, osteoporosis, or

18 osteoporotic fractures pooled analyses, estimates will be expressed as the mean

19 difference, and the pooled odds ratio, relative risk, hazard ratio or beta coefficient and

20 corresponding 95% confidence intervals. The heterogeneity of the studies and the

21 publication bias will be investigated accordingly. To assess the quality and the risk of

22 bias of the included studies, the Newcastle-Ottawa Scale or the Cochrane risk of bias

3

1   assessment tool will be used where appropriate.

2   **Ethics and dissemination** Since no private and confidential patient data will be

3   contained in the reporting, approval from an ethics committee is not required. The

4   results will be published in a peer-reviewed journal. The study raises no ethical issues.

5   **PROSPERO registration number** CRD42019147188

4

1 **Strengths and limitations of the study**

2 ▸ As the first meta-analysis that evaluated the associations between dietary

3 selenium intake or serum selenium concentrations and BMD, osteoporosis, or

4 osteoporotic fractures, the findings of this study will deepen the existing

5 knowledge base on the pathogenesis of osteoporosis, and promote the

6 development of effective preventive or treatment strategies.

7 ▸ Two investigators will perform the study selection, data extraction and quality

8 assessments independently, and disagreements will be resolved by discussions.

9 ▸ Both the quality and the risk of bias will be properly assessed for the included

10 studies by applying the Newcastle-Ottawa Quality Scale or the Cochrane risk of

11 bias assessment tool where appropriate.

12 ▸ Both prospective and retrospective studies will be included in this meta-analysis,

13 which may also incur bias and impact the final results. And the differences in

14 study design and sample characteristics may lead to a high level of heterogeneity.

15 ▸ We wish to investigate the associations between selenium and the different types

16 of primary and secondary osteoporosis, however, such subgroup analysis is

17 difficult or even impossible given the small number of studies will probably be

18 included.

19

5

1   **INTRODUCTION**

2   Bone health affects the ability of the human body to stay active throughout life, and

3   the degradation of bone health can cause considerable morbidity and mortality.[1 2] The

4   various factors related to bone health at different ages play an important role in

5   preventing osteoporosis and its adverse consequences.[3] Bone health is mainly

6   reflected in diseases caused by bone mass loss, such as osteoporosis and fragility

7   fracture.[4 5] Osteoporosis, which is characterized by low bone mass and

8   microarchitectural deterioration of bone tissue, is a systemic skeletal disease that can

9   result in increased bone fragility and increased fracture risk as a consequence.[3 6] With

10   an ageing population, the socioeconomic and medical impact of osteoporosis will

11   increase rapidly. It is estimated that by 2020, there will be over 200 million people

12   worldwide affected by osteoporosis, and the expenses related to osteoporosis will rise

13   to about \$25.3 billion by 2025.[7] Osteoporosis is practically diagnosed by the presence

14   of a fragility fracture or low bone mineral density (BMD) which is a commonly used

15   proxy measure that accounts for approximately 70% of bone strength.[3] However,

16   osteoporosis can occur without a known underlying cause, and its risk factors have

17   not been fully elucidated.

18

19   Nutrition has a significant influence on bone health and adequate nutrition is

20   among the crucial cornerstones of the prevention of osteoporosis.[8] The trace element

21   selenium, as a critical constituent of about 25 selenoenzymes, plays an essential role

22   in a variety of physiological processes and it has been confirmed that the beneficial

6

1   effects of selenium are related to human health.[9][10] Some studies collectively

2   suggested that the preservation of selenoproteins in bone was essential to normal

3   skeletal development.[11] Animal studies have shown that selenium-deprivation can

4   retard growth and change bone metabolism.[12] Such effects are associated with

5   reduced BMD, impaired bone microarchitecture and increased bone resorption.

6   Previous clinical studies have investigated the effects of selenium on bone health,

7   however, the results are inconclusive. Some suggested that serum and dietary

8   selenium were positively correlated with BMD,[13][14] while other showed that neither

9   serum nor dietary selenium was associated with osteoporosis.[15][16] Meanwhile, some

10 case-control studies revealed that the dietary intake of selenium was associated with

11 reduced risk of osteoporotic hip fracture.[17][18]

12

13   Meta-analysis is an effective tool for revealing trends that may not be apparent,

14 and it also helps in establishing clinical policies and guidelines. Thus, we aimed to

15 systematically examine the existing literature in this field to test the hypothesis that

16 dietary or serum selenium concentrations are associate with BMD, osteoporosis, or

17 osteoporotic fractures.

18

19 **METHODS**

20 **Study design**

21 The aim of this meta-analysis is to investigate the associations between dietary intake

22 or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures. This

7

protocol was developed according to the Preferred Reporting Items for Systematic

Review and Meta-Analyses Protocols (PRISMA-P) 2015 Statement,[19] and has been

registered in the international prospective register of systematic reviews PROSPERO

network (registration number: CRD42019147188).

Eligibility criteria

Types of studies

The meta-analysis will include both interventional and observational studies in

humans, inclusive of case-control studies, randomized controlled trials, cross-

sectional studies and cohort studies which focus on the associations between dietary

intake or serum levels of selenium and BMD, osteoporosis, or osteoporotic fractures.

Types of participants

The participants in the included studies must have provided information on dietary

intake or serum levels of selenium, and BMD measures or diagnosis of osteoporosis

or osteoporotic fractures. No age, sex, ethnicity, economic status, geographical

limitations, or education restrictions will be applied.

Types of exposure/intervention

Two main forms of exposure will be included, i.e., dietary intake selenium and serum

levels of selenium.

8

1 Types of outcome measures

2 Primary outcomes will include T-score , BMD values and the prevalence or incidence

3 of osteoporosis. The diagnostic criteria of osteoporosis shall be based on the WHO

4 criteria.[20] T-score between 0 and -1 is considered normal and T-score ≤-2.5 is

5 considered osteoporosis. BMD corresponds to osteopoenia if T-score ranges between

6 -1 and -2.5. Osteoporosis is classified as "primary" and "secondary", and secondary

7 osteoporosis is due to certain clinical disorders independent of age and estrogen

8 deficiency.[21] We will catalog and categorize the different types of primary and

9 secondary osteoporosis according included studies. The secondary outcome will be

10 the prevalence or incidence of osteoporotic fractures. There will be no restriction on

11 site and measuring method, but we will give priority to extracting T-score for analysis

12 rather than to extracting BMD values. When T-score is not available, we will try to

13 analyze BMD measured with Lunar and Hologic machines separately.

14

15 **Information sources**

16 Systematic literature searches will be undertaken across PubMed, Embase and

17 Cochrane Library by applying the specified search strategy to identify relevant studies

18 up to October 2019 on each platform or database. In addition, the references of the

19 retrieved literature will be manually searched. And Grey literature will also be

20 searched included study registries (e.g., ClinicalTrials.gov and google scholar). The

21 relevant studies and systematic reviews will be scanned for additional eligible studies.

22

9

1 **Search strategy**

2 Keyword terms or medical subject heading terms (MESH) will be used to search for

3 eligible studies in the databases mentioned above. The electronic search strategy is

4 presented in **Table 1**. All the search terms will be adapted for different syntax rules of

5 the databases.

6

7 **Study selection**

8 The search results from the three electronic databases will be sent to Endnote. After

9 removing duplicates, two investigators will be responsible for screening the titles and

10 abstracts of all the retrieved literature to identify eligible studies. In case that the

11 eligibility of a study cannot be determined, the full text will be reviewed for inclusion

12 according to prespecified inclusion and exclusion criteria. There will be no restriction

13 on the publication date and language. The study selection process will be summarized

14 based on the PRISMA flow diagram. Disagreements between the two investigators

15 will be resolved by discussing with a third investigator.

16

17 **Data extraction**

18 Two investigators will be engaged to independently extract the following data in a

19 standardized collection form: publication information (author, year of publishing);

20 study information (country of origin, study setting, data sources, study period);

21 demographic information (sample size, age, and sex distribution); exposure

22 information (dietary or serum selenium concentrations); outcome information (T-

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1   score , BMD values, the prevalence or incidence of osteoporosis or osteoporotic

2   fractures). Then, both the adjusted and unadjusted effect sizes (mean difference [MD],

3   odds ratio [OR], relative risk [RR], hazard ratio [HR] or beta coefficient [β]) will be

4   either extracted directly or calculated based on the information in the original studies

5   whenever possible. If the relevant data is not reported in an included study, the

6   missing information will be obtained by contacting the authors directly as far as

7   possible. The two investigators responsible for reviewing the literature will resolve

8   any disagreements through discussions, and a third independent investigator may be

9   involved into the discussion if required.

10

11   **Assessment of risk of bias**

12   The Cochrane risk of bias assessment tool will be used to assess the quality of

13   RCTs,[22] while the Newcastle-Ottawa Quality Scale (NOS) will be used to assess the

14   quality of observational studies.[23] Two investigators will be engaged to conduct the

15   risk of bias assessment independently, and disagreements will be resolved through

16   discussions.

17

18   **Data analysis**

19   Firstly, the characteristics of included studies will be summarized using baseline

20   tables and narrative texts. The proposed study will calculate the MD, the pooled OR,

21   RR, HR or β and the corresponding 95% CIs. Unadjusted risk estimates and adjusted

22   estimates will be pooled in the meta-analysis. Then, Cochrane's Q test and the I^2

11

1 statistics will be used to assess the heterogeneity of the included studies, where p

2 value > 0.05 of the Q statistics and I^2 value < 50% indicate statistical homogeneity.[24]

3 [25] If the included studies are found to be statistically homogeneous, the fixed effects

4 models will be used to pool the data during meta-analysis; otherwise, the random

5 effects models will be used instead. Statistical analyses will be conducted in Review

6 Manager-5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane

7 Collaboration, 2014) and Stata-11.0 (StataCorp LP, College Station, TX) statistical

8 software. Statistical significance is considered at p value < 0.05. Finally, to minimize

9 the heterogeneity between included studies, subgroup analyses based on different age,

10 sex, ethnicity, economic status, geographical limitations, education restrictions, or

11 causes of osteoporosis will be conducted where feasible.

12

13 **Assessment of publication bias**

14 If the number of included studies is greater than 10, a funnel plot will be constructed

15 and the Egger test will be conducted to observe the publication bias. The existence of

16 publication bias is confirmed when the funnel plot shows an asymmetric pattern.

17 Then, the bias, if any, will be explained through discussions after assessment.

18

19 **Patient and public involvement**

20 As our systematic review will be implemented based on published studies, no patients

21 and members of the public will be directly involved. All the data to be used in this

22 study already exists in the published literature and/or the aforementioned sources.

12

1

2 **Ethics and dissemination**

3 As this meta-analysis will be performed based on published studies, and no private

4 and confidential patient data will be contained in the reporting, approval from an

5 ethics committee is not required. The results will be disseminated through publication

6 in a peer- reviewed journal. The study raises no ethical issues.

7

8 **DISCUSSION**

9 The health of the skeletal system is important for elderly people.[1] An in-depth

10 understanding of the relationship between selenium and bone health is useful for

11 designing early life interventions. Selenoproteins expressed in human fetal osteoblasts

12 would appear to protect the bone against oxidative stress, which may contribute to the

13 development of osteoporosis by inhibiting osteoblastic differentiation of bone marrow

14 stromal cells.[26 27] The trace element selenium, as a critical constituent of

15 selenoproteins, is much more likely to be an essential role in the associations between

16 selenium and bone mineral density. To our best knowledge, there are at least 10

17 studies that have investigated the associations between dietary or serum selenium

18 concentrations and BMD, osteoporosis, or osteoporotic fractures. Of them, two

19 studies suggested that serum and dietary selenium were likely to positively correlate

20 with BMD,[13 14] and three studies showed that dietary selenium was negatively

21 associated with osteoporotic fractures.[17 18 28] On the contrary, one study found no

22 association between dietary selenium and BMD,[29] and four studies reported that

13

1   neither serum nor dietary selenium was related to osteoporosis.[15 16 30 31] Contradictory

2   results of these studies might be related to the differences in study design and sample

3   characteristics. So it's still controversial whether the contents of selenium can directly

4   influence BMD and affect the pathogenesis of osteoporosis. The sample size of

5   previous studies might have been too small to achieve sufficient statistical power,

6   which could explain, at least in part, why the statistical difference in some instances

7   was not reached, despite the obvious trends. Therefore, the aim of this systematic

8   review and meta-analysis is to summarize the available evidence to investigate the

9   associations between selenium and bone health. The results of this study will deepen

10   the existing knowledge base on the pathogenesis of osteoporosis, and promote the

11   development of preventive or treatment strategies in this field.

14

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

PATIENT CONSENT FOR PUBLICATION

Not required.

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Conceptualization: Yilun Wang and Dongxing Xie

Data curation: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

Methodology: Jing Wu, Ziying Wu, Hongyi He, Zidan Yang

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1   Writing – original draft: Ning Wang and Dongxing Xie

2   Writing – review & editing: Yilun Wang and Tuo Yang

16

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22   contents of postmenopausal women in Xi'an urban area. *Biol Trace Elem Res* 2009;131:205-14.

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1   **Table 1 Electronic search strategy in Pubmed**

Number	Search terms
1	selenium[mesh] or "selenious acid"[mesh] or selen*[tiab] or selepen[tiab] or organoselen*[tiab] or natriumselen*[tiab] or methylseleninic[tiab] or methylselenium[tiab] or selenomethionin*[tiab] or selenit*[tiab]
2	bone demineralization[mesh] or bone density[mesh] or osteopenia[mesh] or osteoporosis[mesh] or bone densitometry[mesh] or osteoporo*[tiab] or bone densit*[tiab] or bone loss[tiab] or osteomalacia[tiab] or osteodystrophy[tiab] or bone demineralization[tiab] or osteopenia[tiab] or bone mass[tiab] or bone mineral content*[tiab] or bone defect*[tiab] or bone strength[tiab] or BMC[tiab] or "fracture"[mesh] or fracture* [tiab]
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Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	P1
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 (such as PROSPERO) and registration number | P4, P7-8 |

Authors

| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | P1-2 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | P14-15 |

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	P14
Sponsor	#5b	Provide name for the review funder and / or sponsor	P14
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	P14

Introduction

| Rationale | #6 | Describe the rationale for the review in the context of what is | P6-7 |

already known

Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	P8-9

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	P8-9
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	P9
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	P18
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	P10-11
Study records - 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)	P9-10
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any	P10

process		processes for obtaining and confirming data from investigators	
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	P10
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	P8
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	P10-11
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	P10-11
Data synthesis	#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 I2, Kendall's τ)	P11
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	n/a
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	n/a
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within	P11

studies)

Confidence in   #17   Describe how the strength of the body of evidence will be   n/a

cumulative   assessed (such as GRADE)

evidence

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